# Intraocular Lymphoma: Clinical Presentation and Imaging Studies

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## Primary Vitreoretinal Lymphoma/PCNSL-O

### Introduction

Primary central nervous system lymphoma (PCNSL) is a subtype of non-Hodgkin lymphoma confined to the CNS compartments. As per the 2017 World Health Organization classification of hematopoietic and lymphoid tumors, PCNSL is classified as primary diffuse large B-cell lymphoma (DLBCL) of the CNS [1]. The CNS compartments include the brain (deep cortical regions, periventricular regions, and basal ganglia), spinal cord, meninges, and the eyes [2]. Primary intraocular lymphoma is a malignant neoplasm derived from monoclonal proliferations of B- or T-lymphocytes and is classified according to its location into either primary vitreoretinal lymphoma or primary uveal lymphoma. PCNSL-O is the preferred term for vitreoretinal lymphoma to emphasize that it is an ocular variant or subset of primary CNS lymphoma (PCNSL). Those with concurrent CNS and ocular disease may be labeled as (PCNSL-CNS/O) in contrast to patients with CNS only involvement (PCNSL-CNS) at presentation. The involvement of the eye and other CNS compartments varies as ophthalmic manifestations can precede, occur simultaneously with or follow disease in other CNS sites. Sixty percent to 90% of patients with PCNSL-O ultimately involve other CNS compartments, while 20% of patients with PCNSL present with concurrent PCNSL-O [3, 4]. The PCNSL-O often masquerades as infection or inflammation leading to a delay in diagnosis and inappropriate management.

### Epidemiology

Most patients of PCNSL-O are older than 40 years with the usual age of onset being in the late 50s and 60s [5]. The Central Brain Tumor Registry of the U.S. noted an incidence of PCNSL to peak between 75 and 84 years. Most reports of PCNSL-O have found increased incidence in females than in males, in contrast to PCNSL which tends to occur in higher frequency in males [6, 7]. PCNSL-O may be either unilateral or bilateral on initial presentation, but approximately 80–90% of patients will ultimately develop bilateral disease [8, 9]. The median interval between the progression of lymphoma from the eye to other CNS compartments and vice versa varies over a follow-up of 8–29 months [3, 9–11]. In a recent review by Farrall et al. the

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prevalence of ocular involvement at any time during the course of PCNSL was 16% with greater prevalence (69%) of CNS involvement with ocular involvement [2].

## Clinical Presentation

Majority of patients often complain of painless loss of vision and floaters. The rest of the patients are asymptomatic or diagnosed during ophthalmic screening in the setting of known PCNSL. Few rare presentations include exudative retinal detachment, elevated posterior pole lesion, neovascularization, optic neuropathy, and a variety of chorioretinal abnormalities [12].

Ophthalmic examination of anterior segment is usually unremarkable; however, few patients may present with corneal precipitates or mild anterior flare. Chronic waxing and waning course of uveitis may simulate pseudo-hypopyon formation, neovascularization of iris, and secondary glaucoma. Secondary infiltration of the anterior segment may lead to mass formation in the angle or iris. PCNSL-O with T cell variant presents with severe anterior segment inflammation and keratic precipitates [13].

Posterior segment typically presents with significant vitreous inflammation and vitreous cells. The cells typically associated with PCNSL-O are larger than inflammatory cells and organize into strands, clumps, or sheets along with the vitreous fibrils. The lymphoma cells lining along the vitreous gives characteristic "aurora borealis" like appearance [3, 14]. Fundus examination exhibits hallmark features of a flat creamy orange–yellow lesion seen deeper within the sensory retina (Fig. 6.1a, c). Lesions may be single or multiple, confluent or discrete, and may appear as multiple punctate lesions [8, 9, 12]. The presence of multiple subretinal punctate lesions secondary to sub-RPE infiltration with lymphoma cells also known as "leopard spots" is a common finding seen in majority of cases [3] (Fig. 6.2a). Rarely the patient may present with retinal hemorrhages or a single solitary intraocular mass [15]. Associated features include retinal vasculitis, exudative retinal detachment, retinal pigment epithelial atrophy with subretinal fibrosis, disciform scarring, and optic nerve infiltration.

CNS lesions may lead to focal or general symptoms. Generalized signs of increased intracranial pressure (ICP) or more focal symptoms such as weakness, sensory deficits, or aphasia should be evaluated [16].

## Diagnosis

Although clinical examination and ocular imaging are of help in the diagnosis of PCNSL-O, the histopathology examination of the ocular specimens, with demonstration of malignant B lymphocytes in the vitreous or retina still remains the gold standard test to confirm the diagnosis. Immunohistochemistry to characterize lymphocyte type and clonality aids in the management.

### Optical Coherence Tomography (OCT)

The lymphoma cells directly infiltrate the retina and proliferate focally in the pre-Bruch's/sub-RPE space corresponding to the lesions seen on clinical examination as subretinal precipitates.

The typical presenting feature of lymphoma on OCT is the presence of nodular or band hyperreflective spots noted in the pre-Bruch's or sub-RPE space [17, 18] (Fig. 6.1d, e). The infiltrations can be subtle RPE hyperreflective mottling, focal discrete hyperreflective nodularity under RPE or retina, large hyperreflective lesions that create confluent bands of material under the retina, or solid RPE detachments [17, 19].

SD-OCT features such as RPE damage, disruption of the photoreceptor inner segment/outer segment junction, multiple hyperreflective infiltrations in the inner retina, and exudative retinal detachment with subretinal hyporeflective fluid are described in cases with severe PCNSL-O [20]. Vertical hyperreflective lesions extending from the outer to the inner retina have also been described which often preceded the development of subretinal pigment epithelial deposits. In most cases, they resolved with minimal or no scarring after the initiation of chemotherapy [17, 21].

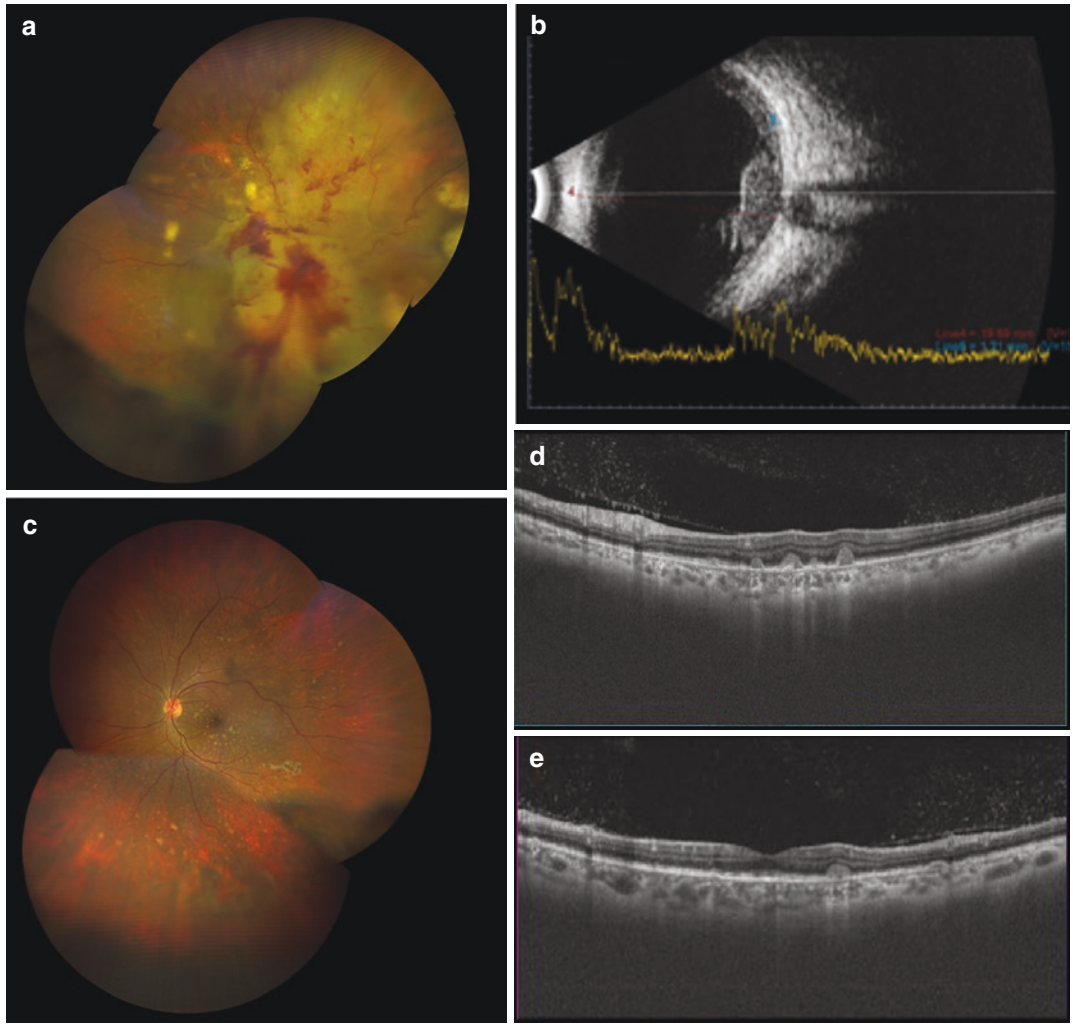


**Fig. 6.1** A 55-year-old woman complaining of diminution of vision associated with floaters in the right eye. Fundus photograph of right eye shows a creamy yellowish elevated lesion at the posterior involving the optic disc with retinal hemorrhages (**a**). The corresponding B-scan demonstrated an elevated subretinal lesion involving the optic nerve head with diffuse flat hyperechoic lesions infiltrating the subretinal space and significant dot echoes in the vitreous cavity (**b**). Fundus photograph of the left eye shows multiple creamy white deposits involving the retinal layers (**c**). Optical coherence tomography shows multiple hyperreflective dots in the vitreous cavity along with nodular hyperreflective elevated lesions underneath the retinal pigment epithelium (RPE) (**d**, **e**)

A study by Dalvin et al. has reported 43% of PCNSL-O eyes have sub-RPE deposits and proposed to be a marker of recurrence, poor visual prognosis, and lower survival time [19]. However, a clear association has not been established. The sub-RPE deposits resolve with chemotherapy and hence OCT is a valuable tool to monitor treatment and to observe for relapse/resolution of PCNSL-O [22].

## Fundus Autofluorescence (FAF)

Fundus autofluorescence demonstrates hypo-autofluorescence corresponding to areas of RPE atrophy and hyper-autofluorescence corresponding to areas with lymphoma cell infiltration [18, 23] (Fig. 6.2b). On multimodal imaging, hyper autofluorescent spots seen on FAF may correlate with the hypofluorescent spots seen on fluorescein angiography (FA; 36%) and the nodular

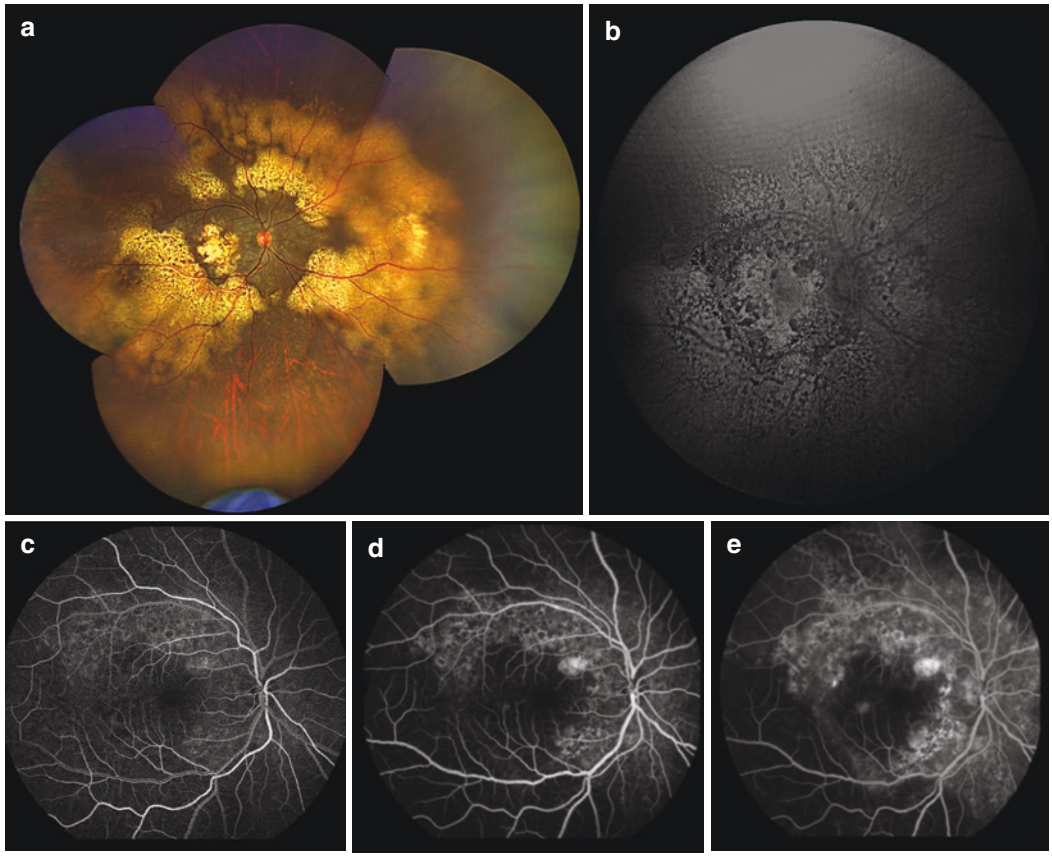


**Fig. 6.2** A 60-year-old man complained of diminution of vision in the right eye. Fundus photograph of the right eye shows ill-defined creamy lesions with yellowish infiltrates located deep in the retina giving a characteristic "leopard skin" pigmentation overlying the lesion (**a**). Fundus autofluorescence shows areas of hypo- with hyperautofluorescence in the posterior pole (**b**). Fluorescein angiography in early, mid, and late phase shows numerous small hypofluorescent lesions corresponding to punctate yellowish lesions in the fundus with few areas of staining in the late phase corresponding to RPE atrophy (**c**–**e**)

hyperreflective spots on OCT (43%) [24]. This concordance was observed in 62% of patients. FAF can also be a valuable tool to document the progression of the disease as well as prognosticate the patient considering the hyperautofluorescence lesions become hypo following complete resolution of the lesions [25].

### B-scan Ultrasound (USG)

B-scan USG is useful to document clusters of condensed punctate echoes as well as elevated chorioretinal lesions and optic nerve widening [26, 27] (Fig. 6.1b).

### Fundus Fluorescein Angiography (FA)

On FA, hypofluorescent spots may represent retinal lymphomatous infiltrates, whereas hyperfluorescent spots represent atrophic lesions secondary to RPE window defects [18] (Fig. 6.2c–e). The punctate hyperfluorescent window defects and hypofluorescent lesions give a characteristic "leopard spot" appearance. In late phase of the disease staining at the level of the RPE may be seen [28].

### Indocyanine Green Angiography (ICGA)

ICGA often shows round clustered hypocyanescent lesions corresponding to the areas of hypo-

fluorescence seen on FA, but it may be completely normal or non-contributory [18, 29]. Other associated features such as perivascular staining or leakage, cystoid macular edema or optic nerve head staining or leakage, are unusual in PCNSL-O and help to distinguish it from patients with chronic uveitis or vitritis of non-malignant etiology.

### Disease Staging

Staging evaluation for the patient is an important part of management. It is usually done in patients with biopsy confirmed diagnosis of PCNSL-O to rule out extraocular sites of involvement like the CNS or testis. MRI brain with contrast along with lumbar puncture for cerebrospinal fluid (CSF) evaluation should be obtained in all patients diagnosed with PCNSL-O since 80% of these patients ultimately develop lymphoma in other areas of their central nervous system [30]. Neurological lesions appear hypo-dense on T1-weighted, hyper-dense on T2-weighted scans with discrete or diffuse borders with characteristic dense and diffuse contrast enhancement. Meningeal enhancement with gadolinium contrast is indicative of leptomeningeal dissemination (LMD). Testicular ultrasound can also be considered in male patients, as the testes represent a relatively immune privileged site where lymphoma can be detected [31]. Serological testing for HIV, hepatitis B and C, plus quantification of serum lactate dehydrogenase (LDH) should also be considered as standard-of-care at baseline.

### Diagnostic Biopsy

Biopsy for the cytological assessment of suspected PCNSL-O is invaluable not only in confirming the diagnosis but also in providing information of prognostic importance [32, 33]. The biopsy specimen can be obtained either from vitreous or subretinal infiltrates and processed for cytological, immunological, and genetic studies [34, 35]. This will be described in detail in the chapter on intraocular biopsy techniques.

### Differential Diagnosis

PCNSL-O is a great masquerader and hence should be distinguished from other infectious and non-infectious uveitic entities such as tuberculosis, sarcoidosis, viral retinitis, retinochoroidal toxoplasmosis, syphilitic retinitis, endophthalmitis, or idiopathic uveitis that present with vitreous cells. The sub-RPE deposits seen on OCT should be differentiated from those seen in age related macular degeneration, polypoidal vasculopathy, and chronic central serous chorioretinopathy. Other neoplastic etiologies such as choroidal metastasis and amelanotic choroidal melanoma can also rarely simulate PCNSL-O lesions.

## Primary Uveal Lymphoma

### Introduction

Unlike PCNSL-O, primary uveal lymphoma is often unilateral and has a benign, indolent course. It is typically a non-Hodgkin's lymphoma, most frequently of B-cell origin. The predominant subtype is extra-nodal marginal zone B-cell lymphoma (EMZL) or mucosa-associated lymphoid tissue (MALT) [36, 37].

### Clinical Features

Patients complain of painless diminution of vision or metamorphopsia due to retinal detachment. They may present with raised intraocular pressure or proptosis when extraocular involvement occurs. Salmon color patches may be seen if subconjunctival or episcleral involvement occurs. Fundus examination shows multifocal yellow-white choroidal infiltration in the early stages and diffuse choroidal thickening in the later stages of the disease [37] (Fig. 6.3a). Choroidal folds and placoid infiltrates may also be seen. The fundus location of these findings is

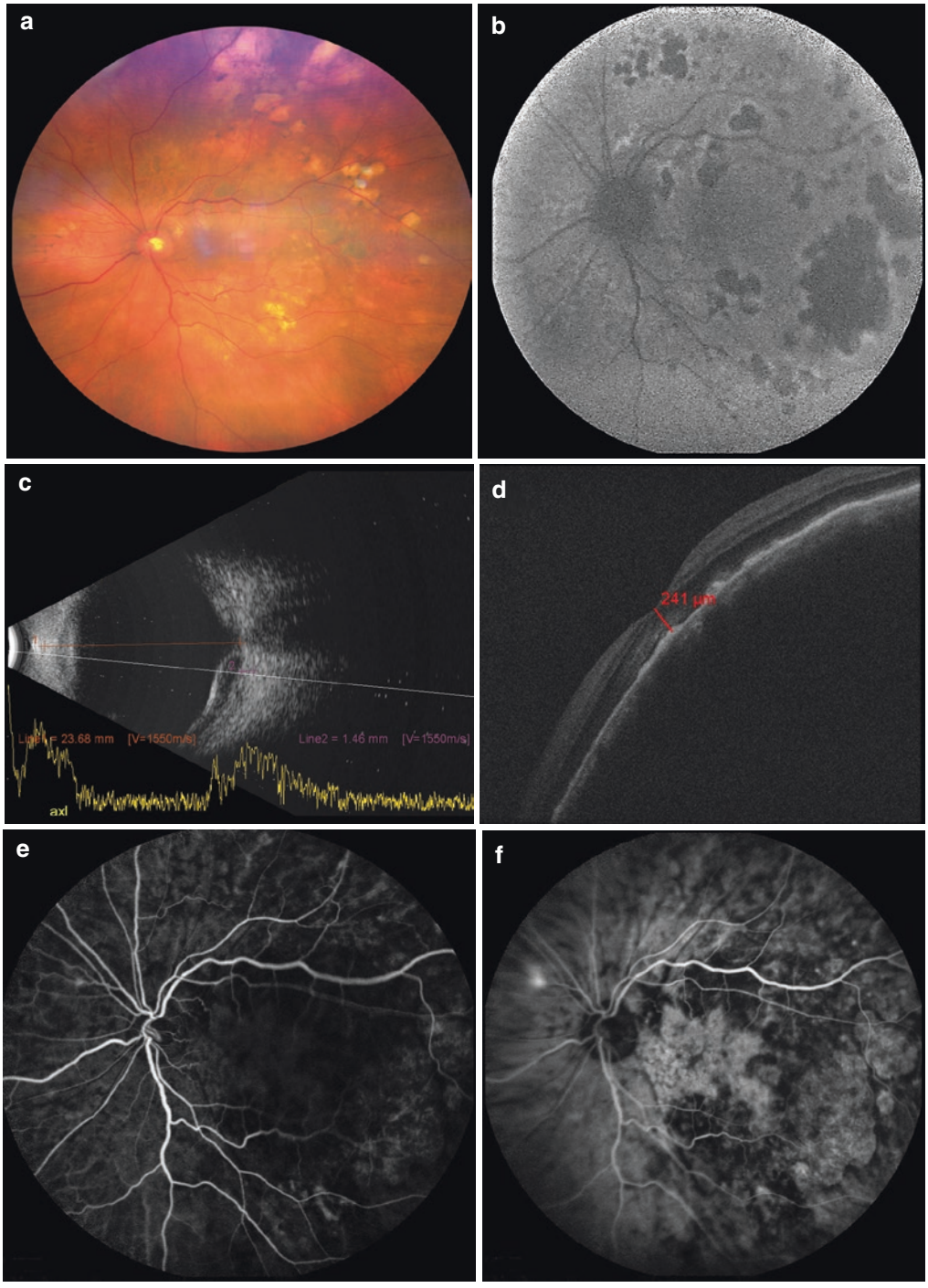


**Fig. 6.3** A 52-year-old woman complained of sudden diminution of vision in the left eye. Fundus photograph of the left eye shows multifocal, yellow choroidal infiltrates involving the posterior pole associated with choroidal thickening (**a**). Fundus autofluorescence shows multiple areas of hypo- with hyper-autofluorescence lesions (**b**). B-scan ultrasound shows diffuse choroidal thickening without extrascleral extension (**c**). Optical coherence tomography shows an elevated choroidal lesion with minimal subretinal fluid and photoreceptor loss (**d**). Indocyanine green angiography in the early and late phase demonstrated hypocyanescent areas corresponding to areas of choroidal infiltrates and hypercyanescent areas in the late phase corresponding to RPE atrophy (**e**, **f**)

typically anterior to the arcades [37]. Vitreous is often clear at presentation. CNS involvement is rare and seen only in advanced disease stages.

## Diagnosis

Diagnosis is usually challenging considering the rare presentation of the disease. Ultrasonography imaging shows a discrete mass with relatively smooth-surface, diffuse choroidal thickening, or presence of subretinal fluid [37] (Fig. 6.3c). B-scan ultrasound is also helpful to detect frank extrascleral extension.

SD-OCT features of choroidal lymphoma show lumpy bumpy choroid with varying topography and increased tumor thickness [38]. Arias et al. have described marked thickening of the choroid with striking choroidal surface undulation and folds imparting an appearance similar to a "sea storm" (seasick appearance) [39] (Fig. 6.3d). Mild tumor infiltration of choroid shows uniform choroidal surface, medium infiltration appears rippled, and thick infiltration appears undulated [40].

Fundus autofluorescence shows multiple areas of hypo- with hyper-autofluorescence lesions corresponding to areas of active choroidal infiltrations and overlying RPE atrophy (Fig. 6.3b). Fluorescein angiography demonstrates early hyperfluorescence in most cases. Few patients have choroidal folds and hypofluorescent spots corresponding to the clinically observed choroidal infiltrates on FA. Indocyanine green angiography reveals hypofluorescent lesions corresponding to the clinically observed choroidal infiltrates [37] (Fig. 6.3e, f).

## Differential Diagnosis

The diagnosis of PUL is challenging as it can simulate other benign and malignant conditions such as choroidal hemangioma, posterior scleritis, uveal effusion syndrome, sarcoidosis, choroidal metastasis, and amelanotic choroidal melanoma. Multimodal imaging and biopsy help to confirm the diagnosis.

## Conclusion

PCNSL-O diagnosis remains challenging, with vague signs and symptoms and difficult diagnostic confirmation. Appropriate suspicion of chronic, treatment-resistant uveitis can aid in earlier detection. Definitive diagnosis still requires the identification of lymphoma cells from the vitreous or subretinal space in case of PCNSL-O and choroid or extraorbital sites in case of uveal lymphoma. Systemic screening and neuroimaging at presentation and follow-up is mandatory considering concurrent or subsequent CNS involvement seen in patients with PCNSL-O.

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