Primary Central Nervous System and Retinal Lymphoma

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7.1 Introduction

Primary lymphoma of the central nervous system (CNS) is considered a variant of extra-nodal non-Hodgkin's lymphoma (NHL), a high-grade B-cell malignancy associated with a median survival ranging from one to 8 years depending on factors such as age and Karnofsky performance status [1]. Primary CNS lymphoma (PCNSL) originates in the brain parenchyma, spinal cord, leptomeninges, and eyes [2]. Formerly used descriptors such as "reticulum cell sarcoma" and "microgliomatosis" are no longer preferred as both misleadingly imply that the lymphoma arises from transformed reticulum or microglial cells. Primary intraocular lymphoma (PCNSL-O) is a variant of PCNSL with predominantly ophthalmic involvement. As vitreoretinal manifestations are the dominant feature, the term primary vitreoretinal lymphoma (PVRL) is commonly used. In contrast, other forms of ocular lymphoma typically affect the adnexal structures or uveal tract. The distinction is important as uveal and ocular adnexal lymphoma are usually low-grade, indolent, B-cell lymphomas that behave similarly to extra-nodal marginal zone lymphoma (EMZL) found elsewhere in the body [3].

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7.2 Pathogenesis

PCNSL is believed to originate from late-germinal center or post-germinal center lymphoid cells; however the neurotropic mechanism by which these cells localize to the CNS remains uncertain [4]. As the CNS and eyes lack lymphatics and lymph nodes, it has been hypothesized that the trafficking of lymphoma cells from the brain to the eye and vice versa involves either invasion of the optic nerve, seeding through shared venous drainage of the brain and eye, or common integrin expression of both organs [2, 4].

There are no known risk factors in immunocompetent individuals; however congenital immunodeficiency and iatrogenic or acquired immunosuppression (AIDS) are risk factors for PCNSL [5, 6]. PCNSL develops in as many as 6 % of patients with AIDS [7, 8]. Epstein-Barr virus infection of B lymphocytes in the absence of T suppressor function (due to immunosuppression) leads to an uncontrolled lymphocytic proliferation. Rare cases of PCNSL may be secondary to human T-cell lymphotropic virus type 1 (HTLV-1) infection [9]. The vast majority of PCNSL are diffuse large B-cell immunoblastic lymphoma [10, 11]. In contrast, PCNSL arising in T cells are composed of small-sized lymphocytes [12].

7.3 Clinical Features

Overall, PCNSL represents about 1–2 % of all cases of lymphoma and 3–5 % of all primary CNS tumors [13–15]. The age-adjusted incidence of PCNSL is approximately 4.8 per million population in the United States [13]. Until a few decades ago, this tumor was best known among patients with AIDS as a manifestation of late-stage disease. With the advent of highly active antiretroviral therapy, the incidence has decreased significantly in this population [16]. However, the incidence among immunocompetent patients has been rising for unclear reasons, although it still remains a rare disease [13]. While PVRL is frequently seen in the setting of PCNSL, the exact incidence is unknown due to the paucity of cases. Between 1999 and 2002, approximately 100 new cases of PVRL were reported in the United States [17].

Among immunocompetent individuals, the peak incidence of PCNSL occurs between the fifth and seventh decades, with a mean age of 60 years at diagnosis [18, 19]. In the immunocompromised population, PVRL occurs in younger individuals [20–22]. Intraocular involvement may precede, occur simultaneously, or follow the CNS disease. In general, intraocular involvement is the presenting feature in PVRL, and subsequent CNS involvement develops in 56–85 % of patients over a period of many months to several years [18, 23, 24]. Conversely, about 25 % of patients with PCNSL have concurrent intraocular involvement [10].

7.3.1 Symptoms

7.3.1.1 Ophthalmic

Patients may be asymptomatic, but up to 50 % present with painless blurred vision, floaters, or both [19, 25]. Bilateral involvement occurs in up to 80 % of cases and is typically asymmetric [24]. Asymptomatic individuals may be diagnosed at the time of ophthalmic screening in the setting of known PCNSL [24]. Owing to the nonspecific nature of the ophthalmic manifestations, a diagnosis of PVRL is difficult to make on clinical grounds alone, and a delay in diagnosis is common. A delay of up to 2 years between the initial presentation and histopathologic confirmation of the PVRL has been reported [23, 25].

7.3.1.2 Central Nervous System

Brain, spinal cord, and meninges either separately or in various combinations can be involved. Solitary involvement of the spinal cord is rarely seen. Personality changes are a common presenting feature because the frontal lobe is the most frequently involved region of the brain. Seizures are an uncommon feature.

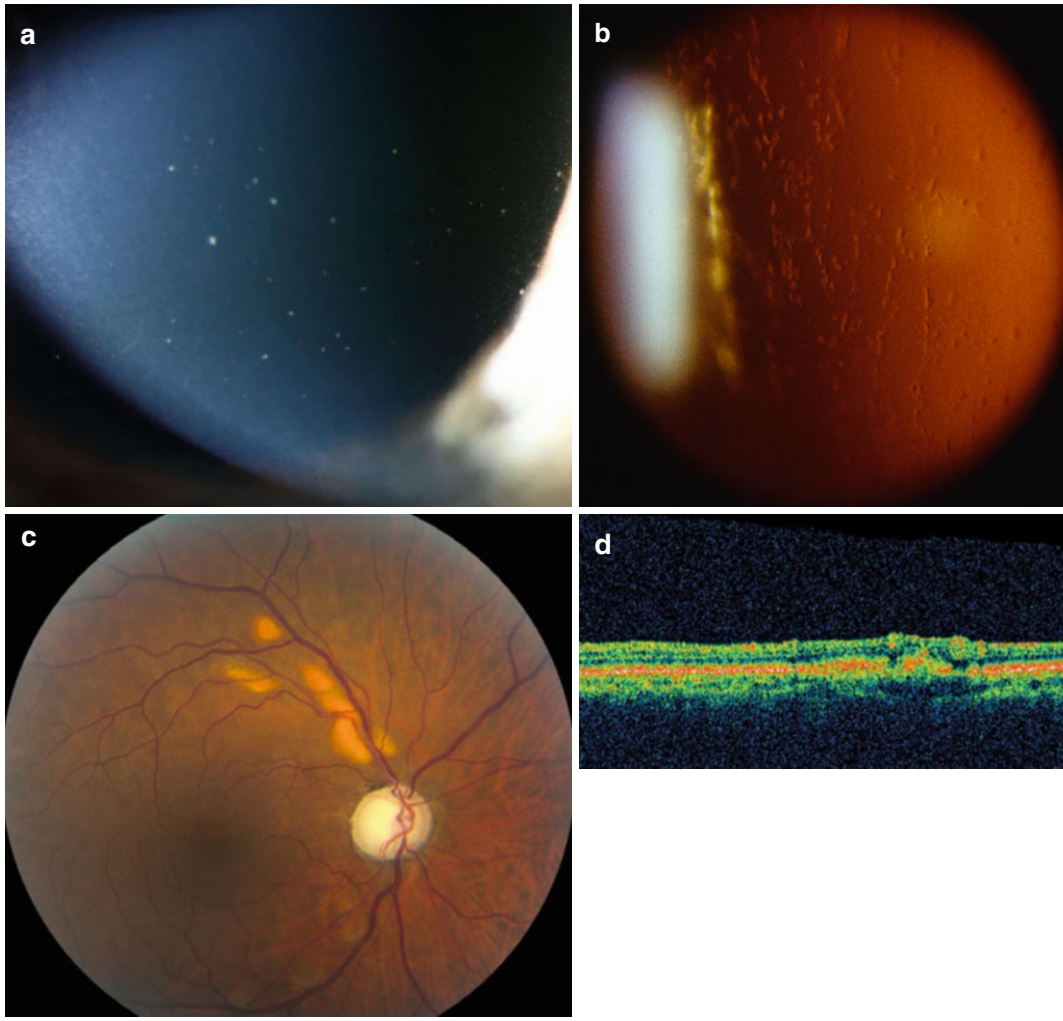

Fig. 7.1 Slit-lamp photograph showing keratic precipitates (**a**), vitreous cells (**b**, retroillumination), and creamy subretinal pigment epithelial infiltrates (**c**, fundus appearance and **d**, optical coherence tomography)

7.3.2 Signs

7.3.2.1 Ophthalmic

The anterior segment findings of PVRL are nonspecific and include keratic precipitates, aqueous cells, and aqueous flare suggestive of inflammation (Fig. 7.1) [25]. The hallmark feature is vitreous cells (50 %), combined anterior and vitreous cells (22 %), and chorioretinitis or subretinal pigment epithelial infiltrates (18 %) [23]. The presence of clumps of cells in the vitreous is a common finding. Multifocal or diffuse chorioretinal infiltrates may be seen with or without vitreous cells. Multifocal subretinal pigment epithelial infiltrates are considered to be pathognomonic (Box 7.1) [26]. Rare findings include perivasculitis, retinal artery occlusion, optic atrophy, and exudative retinal detachment [18, 27–30].

7.3.2.2 Diagnostic Findings of PCNSL-O (Box 7.1)

- Clumps of cells in the vitreous.
- Multifocal or diffuse chorioretinal infiltrates with or without vitreous cells.

- Multifocal subretinal pigment epithelial infiltrates are considered to be pathognomonic.
- Rare findings include choroidal mass, perivasculitis, retinal artery occlusion, and exudative retinal detachment.
- Keratic precipitates, aqueous cells, aqueous flare, and cystoid macular edema are suggestive of inflammation.

7.3.2.3 Central Nervous System

Unlike PVRL, PCNSL is a rapidly growing tumor; the diagnosis is frequently made within a few months of the onset of symptoms. The lesions in the CNS tend to be periventricular in location, thus allowing access to cerebrospinal fluid (CSF) and meninges. An associated meningeal involvement is present in approximately 40 % of cases. Brain lesions can be multifocal, particularly in immunosuppressed individuals.

7.4 Diagnostic Evaluation

Diagnostic evaluation should begin with a thorough history focused on ocular symptoms, changes in cognitive functioning, neurological deficits, and risk factors for immunosuppression. A complete ophthalmic examination of both the anterior and posterior segment is required to assess disease extent and laterality. In the setting of existing PCNSL, the diagnosis of PVRL is straightforward and biopsy of an ophthalmic site is unnecessary if the clinical findings are typical.

The relationship between PVRL and PCNSL is variable with intraocular involvement preceding, occurring simultaneously, or following CNS manifestations. It is therefore imperative that all cases of PVRL should be thoroughly evaluated by a medical oncologist to exclude CNS involvement at the initial diagnosis and periodically thereafter (Fig. 7.2). Conversely, periodic ophthalmic examinations should be part of the diagnostic evaluation and subsequent management of individuals diagnosed with PCNSL.

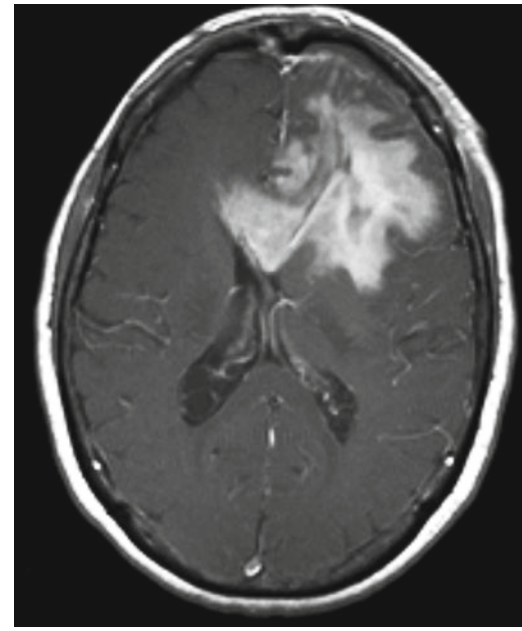

Fig. 7.2 T1-weighted MRI scan of the brain with gadolinium, showing a diffusely enhancing area in the left frontal lobe (Reproduced with permission from Singh et al. [5])

7.4.1 Ophthalmic

In the absence of known PCNSL, the diagnosis of PVRL is based upon clinical, histopathological, and cytological features. Biopsy should be considered in middle-aged or elderly patients with "idiopathic" unilateral or bilateral recurrent uveitis, particularly cases that are unresponsive to steroids. Several diagnostic techniques exist including vitreous, retinal, and subretinal biopsy. Neoplastic cells can be identified by an experienced cytologist, using an array of techniques such as liquid-based cytology, cytospin, and cell block preparations stained with modified Papanicolaou, Giemsa, or standard hematoxylin and eosin stains (Fig. 7.3). Proper and rapid handling of vitreous samples is a must, as aspirates are generally of low cellularity and neoplastic cells undergo rapid lysis.

Most commonly, diagnostic 23-gauge pars plana vitrectomy is performed. It is recommended that an undiluted vitreous sample of about 1–2 ml be collected prior to starting the infusion during vitrectomy [5]. Following

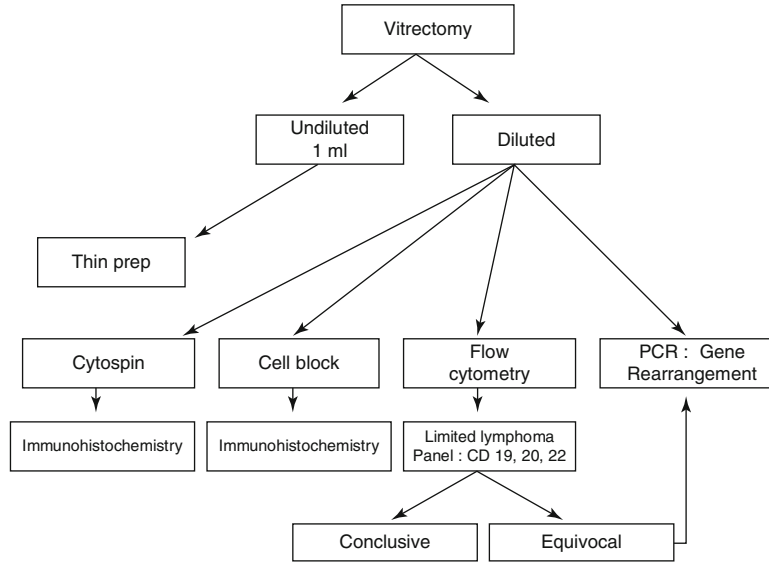

Fig. 7.3 Schema for analysis of vitreous samples for suspected lymphoma. Initial undiluted vitreous specimen (about 1 ml) is processed by ThinPrep for liquid-based cytology because it preserves the cellular details. The diluted vitreous sample is divided into four portions for cytospin, cellblock, and flow cytometry. Gene rearrangement studies are performed if the flow cytometry results are equivocal (Derived from Rishi et al. [33])

collection of the first sample, the infusion fluid is started, and a second diluted specimen is obtained using gentle vitreous cutting [31]. Some centers submit the vitreous cassette to pathology as a third sample [32]. Biopsy specimens should be delivered to the laboratory, without fixative, within 1 h of surgery [33, 34]. It is not uncommon for multiple vitreous biopsies to be performed before a definitive diagnosis is established. There is recent interest in using 25-gauge sutureless vitrectomy for diagnostic purposes, and these techniques may improve patient comfort and decrease operative times. This technique has been used with success in some centers [32].

In the presence of chorioretinal lesions, a chorioretinal or retinal biopsy may be required [11]. Using a standard three-port pars plana vitrectomy, an initial core vitrectomy is performed allowing access to the subretinal infiltrate. Vitreous separation is induced and thorough vitrectomy is performed overlying the biopsy site. A retinectomy large enough to allow entrance of the vitreous cutter and suction tubing is created. With gentle cutting, several samples are obtained [35]. Subretinal aspirates should be placed in a mild cytofixative, such as herpes-glutamic acid buffer-mediated organic solvent protection effect (H.O.P.E.) fixative or Cytolyt (Cytyc) [34].

Approximately 73 % of PVRL cases are diffuse large B-cell lymphomas with characteristic histologic and cytologic features [36]. Tumor cells are two to four times larger than normal lymphocytes, pleomorphic, and have scant cytoplasm [37]. The nuclei may be round, oval, or indented, with conspicuous nuclear membranes, occasional fingerlike protrusions, and multiple, prominent, eccentrically located nucleoli (Fig. 7.4). Mitoses are frequently observed [19]. With the use of electron microscopy, intranuclear inclusions, cytoplasmic crystalloids, and pseudopodal extensions of the cytoplasm, cytosomes, and autophagic vacuoles can be identified [38].

Due to the limited number of cells available for evaluation, it is often difficult to reach a conclusive diagnosis based solely on cytopathological findings. Ancillary histopathologic techniques include immunohistochemistry and flow cytometry to determine immunophenotypes of lymphocytes, gene rearrangement studies using polymerase chain reaction (PCR), and determination of interleukin levels. Greater than 1.0 ratio of interleukin-10 and interleukin-6 has been considered as an indicator of PVRL [39, 40]. However, the clinical utility of determining the interleukin ratio is not clearly established, as cases with PVRL with low interleukin ratios have also been reported [41]. PCR-based tests are used to detect

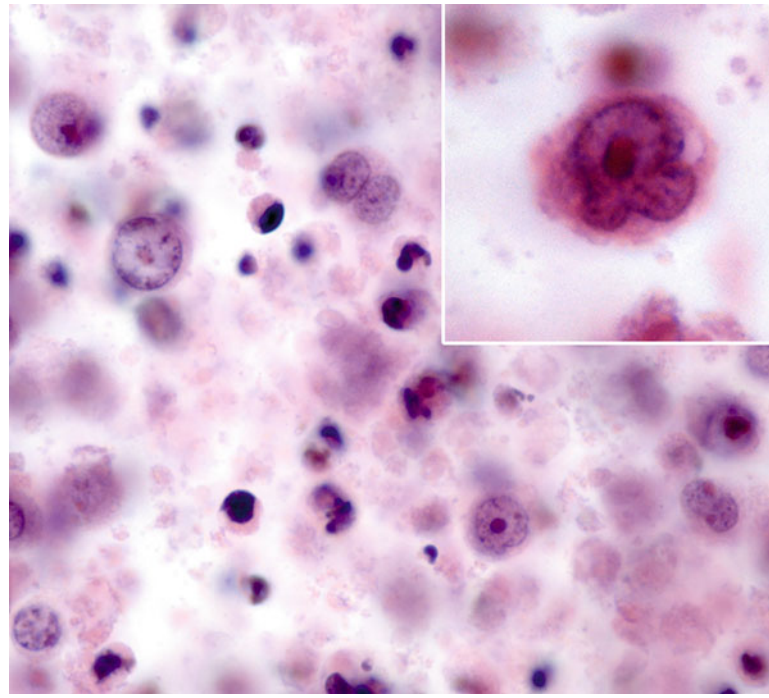

Fig. 7.4 Vitrectomy sample containing large atypical lymphocytes, necrotic lymphoid cells, and nuclear debris. Inset shows characteristic nuclear membrane protrusions and a prominent nucleolus (main figure, Millipore filter, hematoxylin and eosin, original magnification Å ~ 250) (Courtesy of RC Eagle Jr, MD) (Reproduced with permission from Singh et al. [5])

monoclonal proliferation of B lymphocytes, clonal heavy chain immunoglobulin gene rearrangement, bcl-2 gene translocation, and T-cell gene rearrangements [11, 42, 43].

7.4.2 Central Nervous System

Cranio-spinal magnetic resonance imaging (MRI) with gadolinium is the diagnostic procedure of choice. Cranial lesions appear as multiple isointense nodules on T1-MRI and demonstrate characteristic dense and diffuse contrast enhancement (Fig. 7.2). Meningeal enhancement with gadolinium is indicative of meningeal involvement. Many centers also perform CT scans of the chest, abdomen, and pelvis to exclude systemic involvement or systemic origin of the CNS involvement. Cerebrospinal fluid sampling should be performed in every patient with suspected or confirmed PCNSL. Testicular ultrasound examination is recommended in elderly patients because of frequent CNS involvement in testicular lymphomas.

Demonstration of malignant lymphocytes in the CSF is confirmatory for the diagnosis of PCNSL. The CSF shows lymphocytic pleocytosis, raised protein concentration, and normal or low glucose concentration. Visceral involvement is rare at the initial diagnosis but is not uncommon in the terminal stages.

7.5 Differential Diagnosis

In general, all causes of chronic posterior uveitis such as syphilis, sarcoidosis, tuberculosis, and Whipple's disease should be considered in the differential diagnosis. Syphilitic uveitis is a late disease manifestation and may be preceded by dermatologic signs (chancre or rash) and constitutional flu-like symptoms. Ocular syphilis is highly suggestive of CNS involvement and requires systemic therapy. Whipple's disease is a rare, multiorgan infection caused by the bacterium *Tropheryma whipplei.* Middle-aged Caucasian men in the United States and continental Europe are most frequently affected [44, 45]. While common symptoms include weight loss, diarrhea, polyarthralgia, and abdominal pain, extraintestinal manifestations including chronic uveitis can occur. Definitive diagnosis is based upon PCR of vitreous samples.

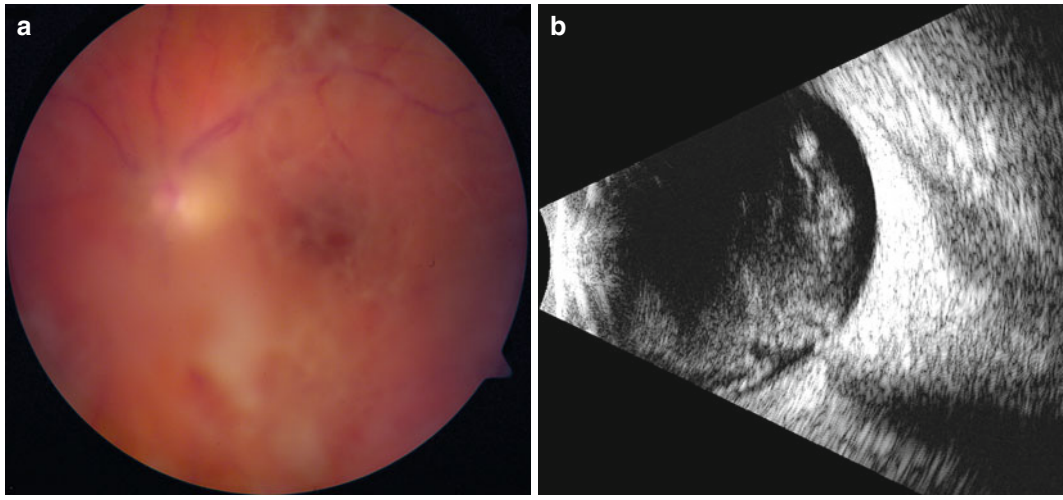

Fig. 7.5 Vitreous amyloidosis can mimic the clinical appearance of vitreoretinal lymphoma (**a**). The vitreous deposits are amorphous, predominantly in the posterior vitreous and overlying the posterior pole (**b**)

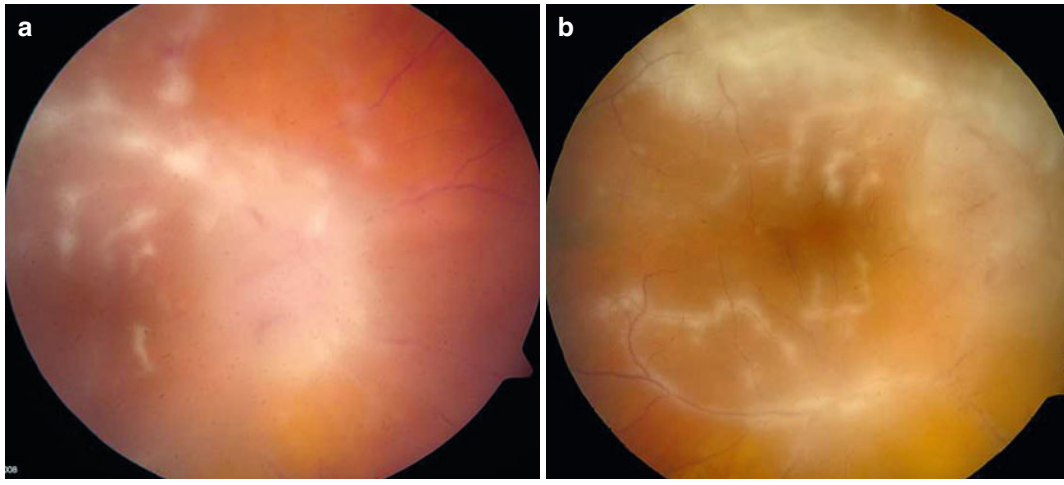

Fig. 7.6 The right optic disc, surrounding retina, and perivascular areas show inflammatory infiltrates in a patient with HTLV-1 retinitis (**a**). Following vitrectomy 6 weeks from initial photographs, the perivascular infiltrates are seen more distinctly (**b**). (Reproduced with permission from Agarwal et al. [50])

Vitreous amyloidosis can also mimic the clinical appearance of PVRL (Fig. 7.5). This rare entity is usually observed in the setting of systemic amyloidosis, although localized ocular involvement is known to occur [46]. Vitreous involvement appears to be linked to the hereditary neuropathies associated with mutation of amyloid protein transthyretin (TTR) [47–49]. Definitive diagnosis is made by vitreous biopsy. The specimen reveals an acellular mix of fibrillar aggregates and focal rosettes. The sample displays metachromatic properties under polarized light when stained with Congo red and toluidine blue, consistent with amyloidosis [46]. Treatment in symptomatic patients consists of total vitrectomy in combination with phacoemulsification and intraocular lens implantation.

Retinal lymphoma in the setting of adult T-cell leukemia/lymphoma (ATL) secondary to HTLV-1 infection may present with retinal vasculitis, retinal infiltration, and disc edema (Fig. 7.6) [50].

Retinal biopsy with subsequent light microscopy evaluation, immunophenotypic studies, and PCR to detect clonal T-cell receptor gene rearrangement may be required for definitive diagnosis [51, 52].

Infiltrative choroidal lesions such as metastatic tumors and amelanotic melanomas can also mimic PVRL. HIV infection predisposes to both opportunistic infections and PVRL; therefore, in an immunosuppressed patient, disseminated choroiditis due to *Nocardia* chorioretinitis and *Pneumocystis* choroiditis should be excluded. When the retina and the vitreous are involved, consideration must be given to entities such as viral or fungal retinitis, acute retinal necrosis syndrome, and toxoplasmosis. Multifocal subepithelial lesions of PVRL should be differentiated from diffuse unilateral subacute neuroretinitis, birdshot retinochoroidopathy, multifocal choroiditis, multiple evanescent white-dot syndrome, and punctate inner choroidopathy. When perivascular infiltrates are present, ocular sarcoidosis and retinal vasculitides must be considered. Patients with systemic lymphomas not arising in the CNS, who develop retinal infiltrates, are more likely to have a superimposed viral or fungal retinitis rather than an intraocular lymphoma [53].

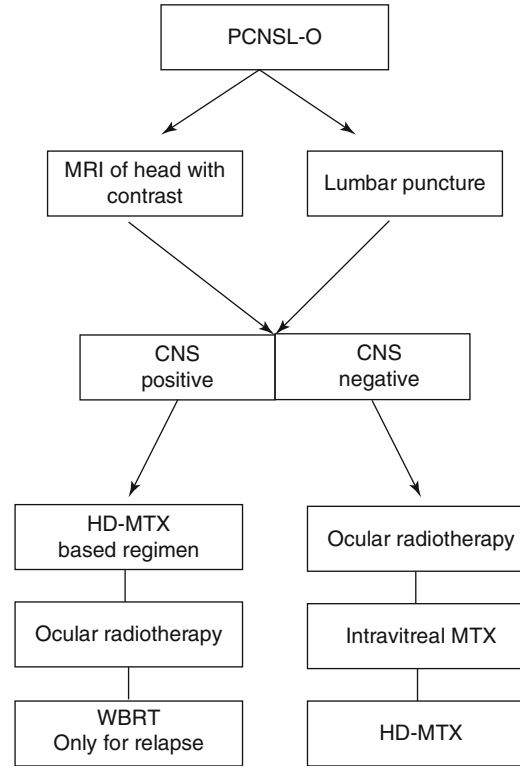

Fig. 7.7 Schema outlining our current approach of management of patients with PCNSL-O. HD-MTX, high-dose methotrexate; WBRT, whole-brain radiation therapy

7.6 Treatment

As PCNSL is very sensitive to corticosteroids, treatment with corticosteroids should be withheld in suspected cases until tissue diagnosis is obtained. The treatment of PCNSL has evolved in the last two decades, and there is a general consensus that regimens containing high-dose methotrexate, with or without whole-brain radiation therapy (WBRT), yield better response rates and outcomes than regimens that do not contain high-dose methotrexate. A schema outlining our current approach of management is shown (Fig. 7.7).

7.6.1 Ophthalmic Treatment

Management of PVRL should be undertaken in partnership with an oncologist who has an expertise in lymphoma. As a high percentage of patients with PVRL eventually develop CNS involvement, some experts recommend that the treatment goal for PVRL must be to eradicate the ocular disease and prevent subsequent CNS involvement. Others favor local therapy for disease confined to the eye with close follow-up and systemic therapy if evidence of CNS disease develops.

7.6.1.1 Local Therapy for PVRL

Local therapies for PVRL include ocular radiation and intravitreal chemotherapy. There has been no trial that has compared these therapies head to head. At the present time, some experts prefer intravitreal chemotherapy while others recommend ocular radiation as first-line therapy. Traditional therapy with ocular radiation (35–40 Gy in ~ 15 divided fractions) controls ocular involvement in the majority of cases [54], but most progress to develop CNS disease (Fig. 7.8) [24]. Irradiation of both eyes (because

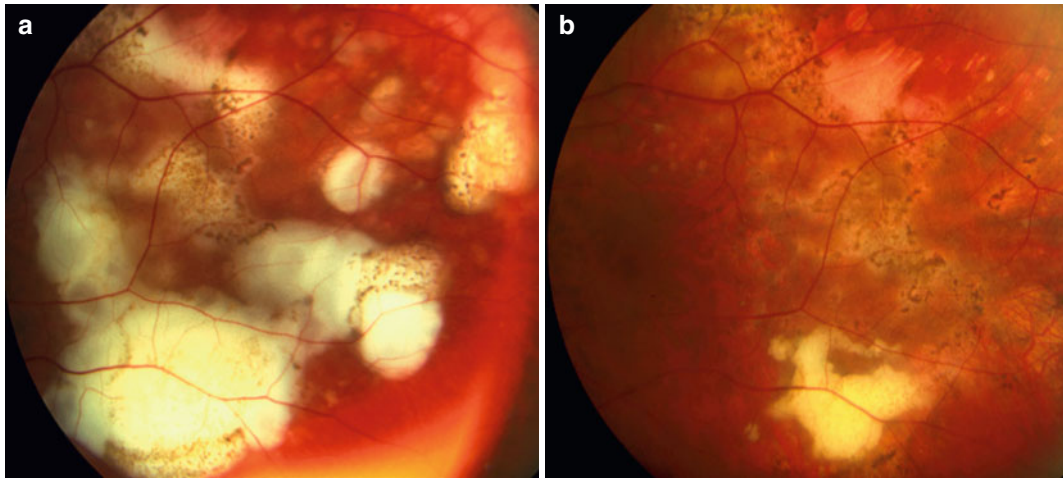

Fig. 7.8 Fundus photograph of the left eye demonstrating multiple creamy subretinal pigment epithelial deposits (**a**). Regression of the subretinal tumors following external beam radiotherapy (**b**, 45 Gy) (Courtesy of S. Seregard, MD.) (Reproduced with permission from Singh et al. [50])

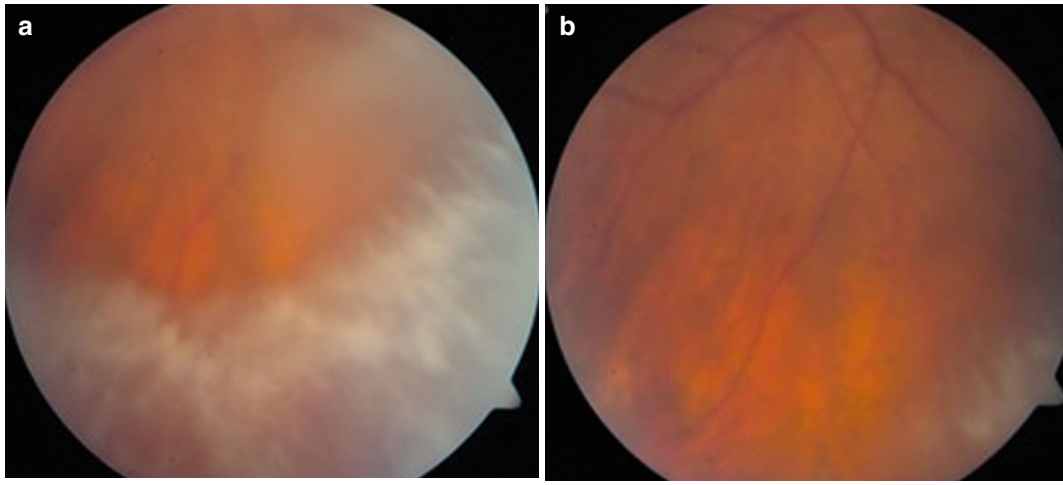

Fig. 7.9 Fundus appearance before (**a**) and after 3 months (induction and consolidation) of treatment with intravitreal methotrexate (**b**). Note dramatic clearance of vitreous cells

of the high incidence of bilaterality) should be strongly considered for patients with proven PVRL. Since radiation therapy to the brain may have significant side effects, its use for prophylaxis in patients without proven CNS involvement is not advisable.

Intravitreal methotrexate as an initial treatment, or for those with recurrence following ocular radiation therapy, has been investigated in a small number of patients with encouraging results (Fig. 7.9; Table 7.1) [5]. In a study involving 16 patients, intravitreal methotrexate (400 μg/0.1 ml) according to a standard induction–consolidation–maintenance regimen was given over a period of 1 year [55]. All patients showed initial tumor control after a maximum of 12 methotrexate injections, but three patients relapsed. The median follow-up was 18.5 months (range 6–35 months). Complications included cataract (73 %), corneal epitheliopathy (58 %), maculopathy (42 %), and vitreous hemorrhage (8 %). No patient had irreversible loss of vision.

Table 7.1 Chemotherapy for treatment of intraocular lymphoma (PCNSL-O)

Author	Year	Cases/eye	Treatment method			Response (%)	Side effects (%)
			Indication	Route	Agent		
Fishburne	1997	47 eyes	Recurrent	Intravitreal with BBB	MTX 400 µg	100	Visual loss 15
Sandor	1998	14		Intravenous and intrathecal	MTX, thiotepa, vincristine, cytarabine	79	Recurrence 71 Neurotoxicity 14
Soussain	2001	22	Refractory/recurrent	Intravenous	Multiagent chemotherapy with stem-cell rescue	75	Recurrence 10 Neurotoxicity 35
Smith	2002	16/26 eyes	Initial	Intravitreal	MTX 400 µg	100	Recurrence 12 Cataract 73 Epitheliopathy 58 Maculopathy 42 Vitreous hem 8 Optic atrophy 4 Endophthalmitis 4
Batchelor	2003	9	Initial	Intravenous	MTX High dose	78	Recurrence 40
Frenkel	2008	26/44 eyes	Initial/recurrent	Intravitreal	MTX 400 µg	91	Conjunctival hyperemia and some form of keratopathy 100
Soussain	2008	43	Refractory/recurrent	Intravenous	Multiagent chemotherapy with stem-cell rescue	61	Treatment-related mortality ~10
Jahnke	2009	10	Initial/recurrent	Intravenous/oral	Ifosfamide or trofosfamide	90	Thrombocytopenia or leucopenia 40

BBB blood–brain barrier disruption with mannitol, *MTX* methotrexate
Excluding single-case reports

Recently, Frenkel and colleagues reported their experience with intravitreal methotrexate in the largest series to date. They demonstrated clinical remission after a mean of 6.4 ± 3.4 (range, 2–16) injections of methotrexate, in 44 eyes of 26 patients with PVRL [56]. Intravitreal rituximab has been shown to penetrate the entire retina, and in recent times there has been interest in exploring its role in PVRL. Small studies have demonstrated the activity of intravitreal rituximab monotherapy for PVRL. There have been early reports of efficacy of combination of intravitreal methotrexate and rituximab, and this combination remains investigational [57]. This combination approach is attractive as it may decrease the need for multiple methotrexate injections and may help in reducing toxicity.

7.6.1.2 Systemic Therapy for PVRL

Disease relapse in the CNS is a major issue, particularly after local treatment with ocular radiotherapy or intravitreal chemotherapy. Systemic chemotherapy offers the advantage of simultaneous treatment of both ocular and microscopic intracranial disease (Table 7.1). High-dose methotrexate forms the backbone of treatment in PCNSL patients. Batchelor and colleagues reported their experience in nine patients with intraocular involvement of lymphoma treated with methotrexate at 8 g/m^2 [58]. Potentially cytotoxic, micromolar levels of methotrexate were detectable in the aqueous and vitreous humor in most patients. An intraocular response was reported in seven patients, with complete response (CR) in six and a partial response (PR) in one. Efficacy of ifosfamide or trofosfamide was assessed in a recent, prospective, single-center study of ten patients with PVRL that were treated with these therapies. There was a 100 % response rate (nine CRs, one PR) observed that resulted in a median overall survival (OS) of 32 months. Of the seven relapses seen in the study, five were ocular and two occurred in the CNS.

Unlike PCNSL, experience with combination chemotherapy in PVRL is extremely limited. Sandor and colleagues reported 100 % response rate (11 CRs, three PRs), in 14 patients (five with intraocular involvement) in patients treated with a complex treatment regimen consisting of intravenous methotrexate, vincristine, and thiotepa as well as intrathecal methotrexate and cytarabine. Although a high initial response was seen, the duration was limited and additional therapy was required at relapse.

High-dose chemotherapy followed by stem-cell transplantation has been studied in a limited number of trials that have included small numbers of patients with ocular disease. These studies have included both newly diagnosed patients and patients with refractory or recurrent disease [59–61]. Although ocular response has been reported with this aggressive approach, high relapse rates along with observed toxicities associated with stem-cell transplantation make this approach investigational at the current time.

In a report of 221 immunocompetent patients with PCNSL and/or PVRL, Grimm and colleagues reported no difference in disease progression rates or OS in patients treated with local therapy versus those who received systemic therapies. The report, although the largest series reported, was an uncontrolled, multicenter, and retrospective study that utilized different treatments depending on the preference of the treating physician [62]. Thus, as noted above, there is no consensus on treatment of PVRL. An individualized patient-specific approach should be taken (Box 7.2).

7.6.1.3 Treatment options for PCNSL (Box 7.2)

- External beam radiotherapy alone or combined with systemic chemotherapy has been used in treatment of PVRL. Side effects include radiation retinopathy and radiation maculopathy, and there is risk of recurrence of PVRL and PCNSL.
- Treatment options that include intravitreal chemotherapy using methotrexate and/or rituximab are increasingly been employed

in controlling the PVRL and avoid the side effects of EBRT. Major vision-threatening side effects have not been reported with intravitreal chemotherapy.

- Methotrexate-containing multiagent chemotherapy regimens are the preferred therapy for treatment of central nervous system disease. The timing and dose of whole-brain radiotherapy is unclear, given the significant risks of late neurotoxic effects.

7.6.2 Central Nervous System

Until recently, whole-brain radiotherapy was the mainstay of treatment, which improved the median survival to about 12–18 months from 4 months in untreated patients [63]. In 1992, trials using a combination of methotrexate-based chemotherapy and radiotherapy first reported an improved median survival of about 40 months [63]. However, the combination of whole-brain radiotherapy and chemotherapy is associated with a significant risk of neurotoxicity in older individuals [64]. Therefore, chemotherapy alone

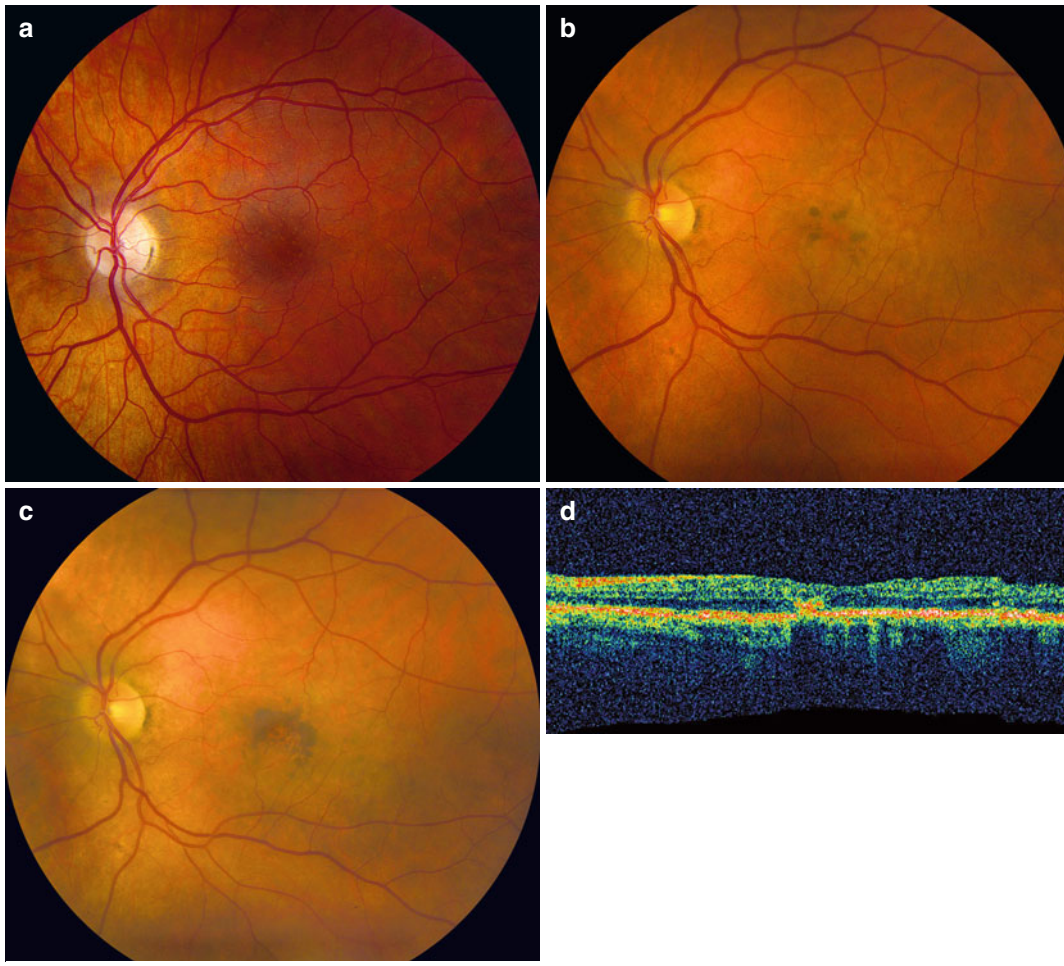

Fig. 7.10 Color photographs of left fundus from two patients with primary central nervous system lymphoma treated with blood–brain barrier disruption therapy demonstrating the spectrum of hyperpigmentation and retinal pigment epithelium (RPE) loss within the macula. (**a**) Mild and moderate severity (**b**). Four months after completion of treatment (patient **b**), note progression of retinal pigment epithelium changes(**c**). Optical coherence tomography showing irregular thickening of the retinal pigment epithelium (Reproduced with permission from Galor et al. [66])

is the initial treatment of choice in older individuals (60 years) [63]. As the blood–brain barrier is a limiting factor, which restricts drug entry into the CNS, various strategies to circumvent the blood–brain barrier have been evaluated. These include the use of high doses of chemotherapy, intrathecal drug delivery, intraventricular drug delivery by a reservoir, and temporary disruption of the blood–brain barrier (BBBD) with mannitol infusion [63]. In a large multi-institutional experience of 149 newly diagnosed PCNSL patients (with no prior WBRT) that were treated with osmotic BBBD and intra-arterial (IA) methotrexate, an overall response rate of 82 % (58 % CR; 24 % PR) was reported with a median PFS and OS of 1.8 and 3.1 years respectively [65]. Maculopathy is an ocular complication associated with BBBD with mannitol (Fig. 7.10) [66]. The characteristic findings include RPE clumping in the macula and hyperpigmentation in the foveal region associated with variable RPE atrophy. Mannitol maculopathy is typically bilateral but often asymmetric. Unlike age-related wet macular degeneration, there is absence of subretinal fluid or macular edema. The maculopathy may progress, even after completion of treatment.

In recent years high-dose methotrexate-containing multiagent regimens have been commonly adopted as the preferred treatment option for this disease entity. The timing and dose of whole-brain radiotherapy is still unclear, given the significant risks of late neurotoxic effects, and there is a large ongoing cooperative group study to evaluate the role of radiation in upfront treatment of PCNSL [67].

7.7 Prognosis

Survival after whole-brain radiation therapy ranges from 12 to 18 months. The survival increases to an average of 36–48 months following high-dose methotrexate-based chemotherapy regimen alone or chemotherapy followed by radiation [18, 23, 54]. Age less than 60 years at diagnosis and high initial performance status are well recognized favorable prognostic factors in PCNSL [1, 68].The International Extranodal Lymphoma Study Group also devised a prognostic scoring system comprising of 5 variables associated with poor prognosis that include age greater than 60 years, Eastern Cooperative Oncology Group performance status greater than 1, increased CSF protein level, increased serum lactate dehydrogenase level, and tumor involvement of the deep regions within the brain (basal ganglia, periventricular regions, brain stem, or cerebellum) [69]. Involvement of brain stem and meninges implies an unfavorable prognosis [68]. Expression of p53, c-Myc, or Bcl-6 also suggests a poor prognosis [70]. The presence or absence of retinal involvement in the setting of existing CNS disease is not a prognostic factor that influences survival [68].

7.8 Summary

Primary lymphoma of the central nervous system (CNS) is considered a variant of extra-nodal non-Hodgkin's lymphoma (NHL), a high-grade B-cell malignancy. There are no known risk factors in immunocompetent individuals; however congenital immunodeficiency and iatrogenic or acquired immunosuppression (AIDS) are risk factors for PCNSL. Brain, spinal cord, and meninges either separately or in various combinations can be involved. Patients may be asymptomatic, but up to 50 % present with painless blurred vision, floaters, or both. The hallmark diagnostic feature is vitreous cells (50 %), combined anterior and vitreous cells (22 %), and chorioretinitis, or subretinal pigment epithelial infiltrates (18 %). Several diagnostic techniques exist including vitreous, retinal, and subretinal biopsy. There is a general consensus that regimens containing high-dose methotrexate, with or without whole-brain radiation therapy (WBRT), yield better response rates and outcomes than regimens that do not contain high-dose methotrexate. Disease relapse in the CNS is a major issue, particularly after local treatment with ocular radiotherapy or intravitreal chemotherapy. Management should be undertaken in partnership with an oncologist who has an expertise in lymphoma.

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