7 Primary Central Nervous System and Retinal Lymphoma

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Introduction

Primary central nervous system lymphoma (PCNSL) is an aggressive, extra-nodal non-Hodgkin's lymphoma (NHL). This predominantly B-cell malignancy is associated with a median survival ranging from 1 to 8 years depending on factors such as age and Karnofsky performance status [1]. PCNSL originates in the brain parenchyma, spinal cord, leptomeninges, and eyes. Formerly used descriptors such as "reticulum cell sarcoma" and "microgliomatosis" are no longer used as both misleadingly imply that the malignancy arises from transformed reticulum or microglial cells. Vitreoretinal lymphoma (VRL) is a variant of PCNSL characterized by ophthalmic involvement. The distinction between VRL and other forms of ocular lymphoma that affect the adnexal structures and/or uveal tract is important, as the latter are most commonly indolent, B-cell lymphomas that behave similarly to their systemic counterparts [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 central nervous system (CNS) remains uncertain. As the CNS and eyes lack lymphatic networks, 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 or seeding through a shared vascular supply [3].

Animal models have the potential to improve our current understanding of lymphoma pathogenesis in humans. Early work in this area focused on murine models created by intraperitoneal or intravitreal injection of T-cell lymphoma, while more recent murine models have used human B-cell lymphoma cell lines in order to more closely mimic the human disease state [4]. Intravitreal injection of human B-cell lymphoma (cell line CA46) into severe combined immunodeficient (SCID) mice sacrificed at sequential time points revealed tumor infiltration first at the retinal surface, followed by migration through

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the retina and progression through the subretinal space, and eventually spread to the choroid and the CNS [5]. While choroidal involvement is seen in animals, lymphoma cells typically do not cross Bruch's membrane in humans.

There are no known risk factors in immunocompetent individuals; however, congenital immunodeficiency and iatrogenic or acquired immunosuppression such as human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) are risk factors. PCNSL develops in as many as 6% of patients with AIDS [6]. Epstein-Barr virus infection of B lymphocytes in the absence of T-cell suppressor function (due to immunosuppression) leads to an uncontrolled lymphocytic proliferation [7]. While the vast majority of PCNSL are of the diffuse large B-cell lymphoma subtype, rare cases can be secondary to human T-cell lymphotropic virus type 1 (HTLV-1) infection [8].

Clinical Features

Epidemiology

PCNSL represents about 1–2% of extra-nodal lymphomas and 4–6% of primary brain tumors. The age-adjusted annual incidence of PCNSL is approximately 4.8 per million population in the United States. 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 (HAART), the incidence has decreased significantly in this population. However, the incidence among immunocompetent patients has been rising, for unclear reasons [9]. While VRL is frequently seen in the setting of PCNSL, the incidence is unknown due to the paucity of cases. Between 1999 and 2002, approximately 100 new cases of VRL were reported in the United States [10].

Among immunocompetent individuals, the peak incidence of PCNSL occurs between the fifth and seventh decades, with a mean age of 60 years at diagnosis [11]. In the immunocompromised population, the disease occurs in younger individuals. Intraocular involvement may precede, occur simultaneously, or follow the CNS disease. Intraocular involvement is the presenting feature in VRL, and subsequent CNS involvement develops in 56–85% of patients over a period of 8–29 months [12]. Conversely, nearly 25% of patients with PCNSL will have concomitant vitreoretinal lymphoma at the time of CNS diagnosis [13].

Symptoms

Ophthalmic

Patients may be asymptomatic, but up to 50% present with painless blurred vision, floaters, or both. Bilateral involvement occurs in up to 80% of cases and is typically asymmetric [12]. Asymptomatic individuals may be diagnosed at the time of ophthalmic screening in the setting of known PCNSL. Owing to the nonspecific nature of the ophthalmic manifestations, a diagnosis of VRL is difficult to make on clinical grounds alone, and delay in diagnosis is common. An average time of 2 years from onset of symptoms to histopathologic confirmation of diagnosis of 2 years has been reported [14].

Central Nervous System

The brain, spinal cord, and leptomeninges either separately or in various combinations can be involved. Solitary involvement of the spinal cord is rare. 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.

Clinical Features

Ophthalmic

Anterior segment findings in VRL are rare and are also nonspecific but include keratic precipitates, aqueous cells, and aqueous flare. The hallmark feature is vitreous cells (present in up to 50% of cases), combined anterior and vitreous cells (22% of cases), and subretinal pigment epi-

thelial (RPE) infiltrates (18% of cases) [15]. Clumps of cells in the vitreous with an "aurora borealis" appearance are a common finding. Multifocal subretinal pigment epithelial infiltrates are considered to be pathognomonic (Fig. 7.1). Rarer findings include perivasculitis, retinal artery occlusion, optic atrophy, and exudative retinal detachment (Table 7.1).

Central Nervous System

PCNSL is a rapidly growing tumor, and diagnosis is often established 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 leptomeninges. Leptomeningeal disease is present in up to 40% of cases [16]. Brain lesions can be multifocal, particularly in immunosuppressed individuals.

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 segments is required to assess disease extent and laterality. Fundus auto-

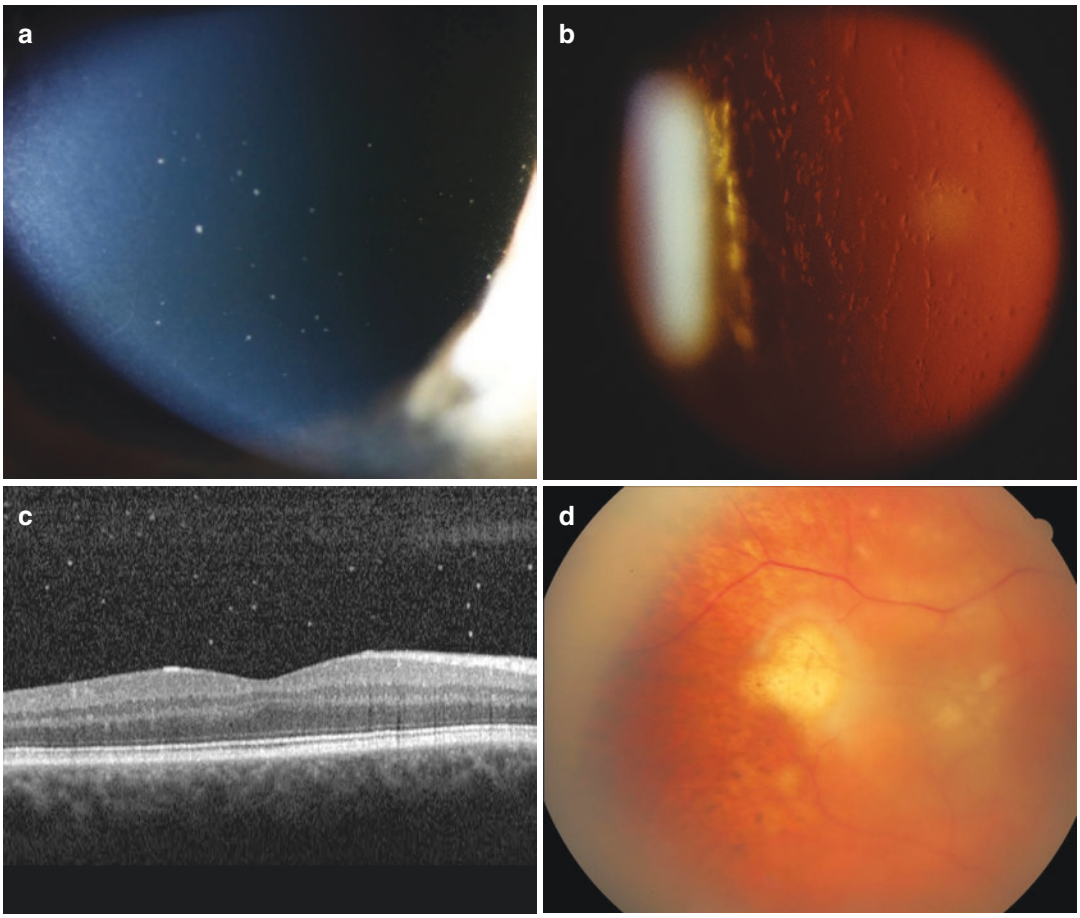

Fig. 7.1 Slit-lamp photograph showing keratic precipitates (**a**), vitreous cells on transillumination (**b**), large clumped vitreous cells on optical coherence tomography (**c**), creamy subretinal pigment epithelium infiltrates on ophthalmoscopy (**d**), and subretinal pigment epithelium infiltration by optical coherence tomography (**e**). Fluorescein angiography reveals multiple hyperfluorescent pinpoint foci scattered throughout the fundus (**f**)

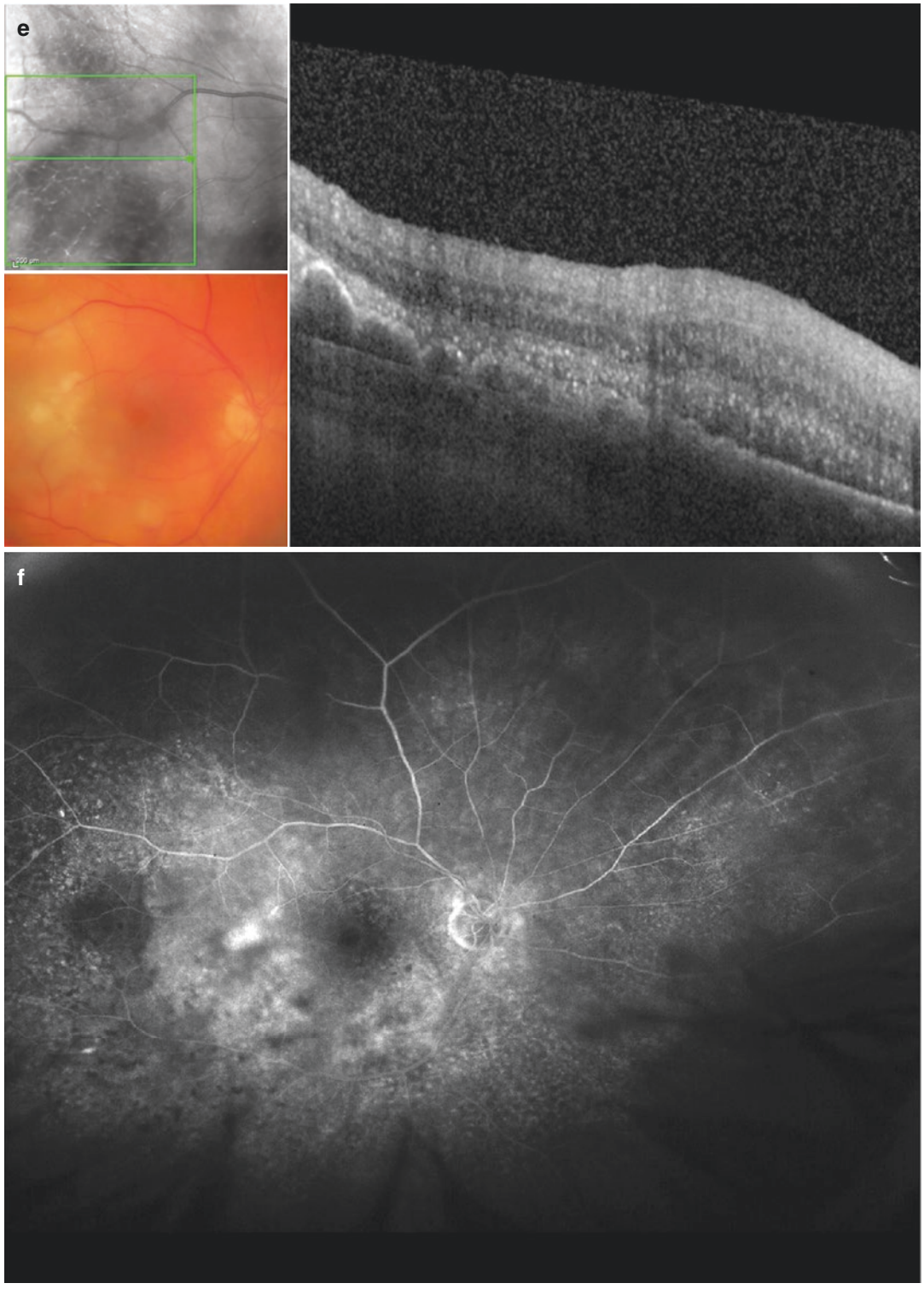

Fig. 7.1 (continued)

Table 7.1 Chemotherapy for treatment of primary vitreoretinal lymphoma (VRL)[a]

Author	Year	Cases/ eyes	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 + 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)
Kitzmann	2007	5	Initial	Intravitreal + intravenous	Rituximab + MTX	100	None
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 leukopenia (40)
Hashida	2012	20 eyes	MTX intolerance	Intravitreal	Rituximab	100	IOP increase (60) Iridocyclitis (35)
Larkin	2014	48 eyes	Initial/ refractory	Intravitreal	Rituximab and/or MTX	65	Recurrence (23)
Riemens	2015	21	Initial	Intravitreal + intravenous	Multiagent chemotherapy	—	Recurrence (36) Renal failure (10)
Akiyama	2016	10	Initial	Intravitreal + intravenous	MTX	100	Recurrence (40)
Shields	2017	3 eyes	Initial	Intravitreal	Melphalan	100	None
Abu Samra	2018	51 eyes	Initial	Intravitreal + intravenous	MTX and/or rituximab	100	—

Abbreviations: BBB blood-brain barrier disruption with mannitol, *MTX* methotrexate
[a]Excludes single-case reports

fluorescence (AF) is helpful in diagnosis and in monitoring progression of vitreoretinal lymphoma [17]. Active lesions appear as hyper-AF lesions as compared with inactive (atrophic) lesions that appear as hypo-AF. In general, hyper-AF lesions correspond with hypofluorescent appearance on the fluorescein angiography [18]. The hyper-AF is explained on the basis of RPE and photoreceptor disruption by the sub-RPE lymphoma infiltrates, which can be appreciated on optical coherence tomography (OCT) [19]. After treatment, as active lesions become inactive (atrophic), the AF pattern correspondingly changes from that of hyper-AF to hypo-AF (Fig. 7.2) [20].

The relationship between VRL and PCNSL is variable with intraocular involvement preceding, occurring simultaneously, or following CNS manifestations. It is therefore recommended that

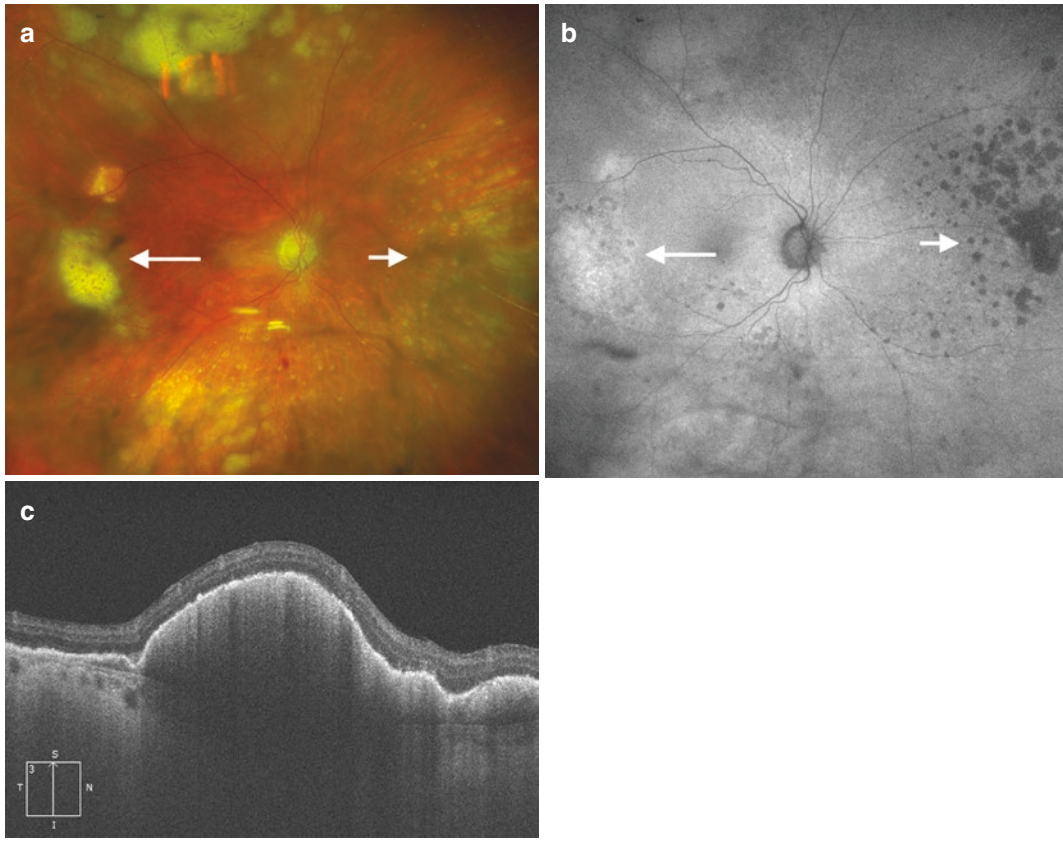

Fig. 7.2 Fundus photograph of vitreoretinal lymphoma (**a**). Note active lesion (large arrow) and inactive atrophic lesions (small arrow). With AF using green laser source (532 nm, Optos system), the active lesion appears hyper-AF (large arrow) as compared with inactive (atrophic) lesions that appear hypo-AF (**b**, small arrow). The hyper-AF is explained on the basis of RPE and photoreceptor disruption by the sub-RPE lymphoma infiltrates (**c**)

individuals with VRL undergo a thorough evaluation by a medical oncologist to exclude CNS involvement at the time of initial diagnosis and periodically thereafter (Fig. 7.3). Similarly, periodic ophthalmic examinations should be part of the diagnostic evaluation and subsequent management of individuals diagnosed with PCNSL.

Ophthalmic

In the absence of known PCNSL, the diagnosis of VRL may be suspected based upon clinical features, but diagnosis relies on confirmatory histopathology. Biopsy should be considered in middle-aged or elderly patients with "idiopathic" uveitis, particularly in cases that are initially responsive to steroids but are recurrent. 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. 7.4). When analyzing fresh samples, proper and rapid handling of vitreous samples is critical, as aspirates are generally of low cellularity and neoplastic cells undergo rapid lysis. The laboratory should therefore be informed of the impending arrival of the specimen even before the biopsy is performed. If a delay of more than 1 h is anticipated, then a mild fixative, such as CytoLyt, should be used.

Diagnostic pars plana vitrectomy is frequently performed for diagnostic confirmation. A com-

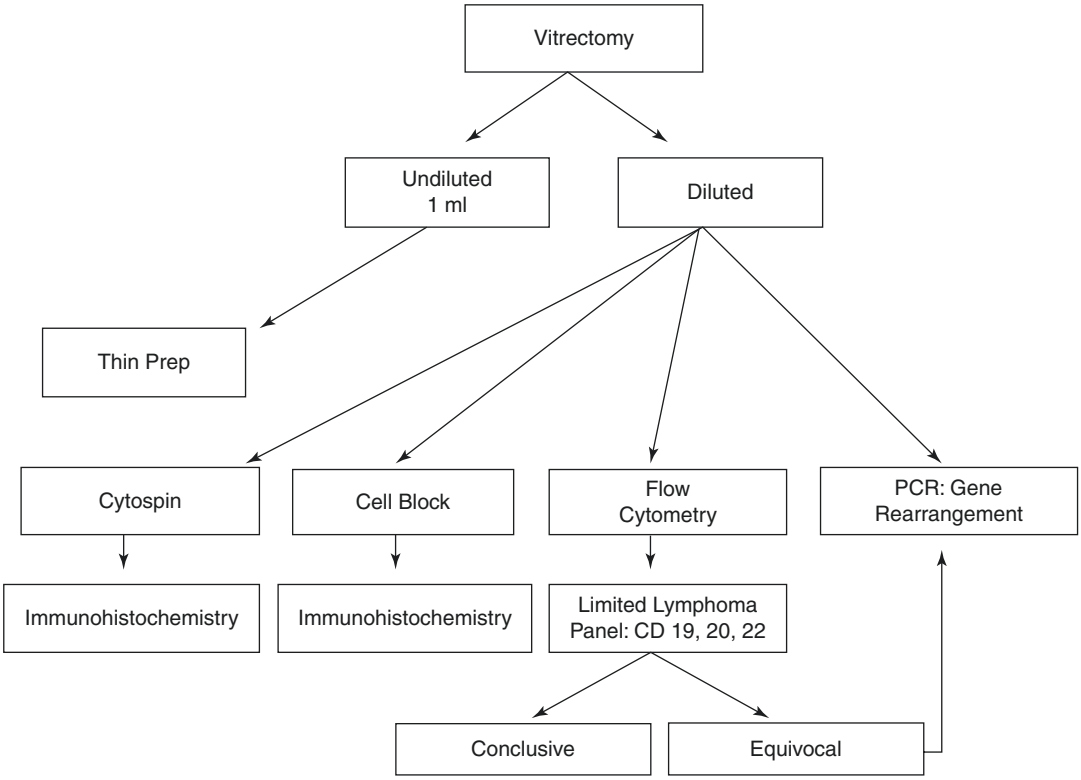

Fig. 7.3 Schema for analysis of vitreous samples for suspected lymphoma. Initial undiluted vitreous specimen (about 1 ml) is processed by ThinPrep for liquid-based cytology because it preserves the cellular details. The diluted vitreous sample is divided into four portions for cytospin, cellblock, and flow cytometry. Gene rearrangement studies are performed if the flow cytometry results are equivocal. (Based on data from Rishi et al. [21])

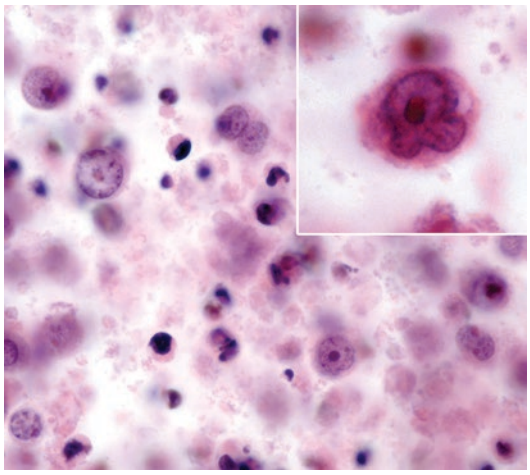

Fig. 7.4 Vitrectomy sample containing large atypical lymphocytes, necrotic lymphoid cells, and nuclear debris. Inset shows characteristic nuclear membrane protrusions and a prominent nucleolus (main figure, Millipore filter, hematoxylin, and eosin; original magnification Å ~ 250). (Courtesy of Ralph C. Eagle Jr., MD)

mon technique is to obtain an undiluted vitreous sample of about 1–2 ml prior to the start of the infusion during vitrectomy. Some surgeons indent the globe to do this and others inject air. Following collection of the first sample, the infusion fluid is started, and a second diluted specimen is obtained using gentle vitreous cutting. Some centers submit the vitreous cassette as a third sample. If being processed fresh, specimens should be delivered to the laboratory within 1 h of surgery. Failure is not uncommon. Multiple vitreous biopsies may need 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 [22].

When vitreous cells are minimal or absent and subretinal pigment epithelial infiltrates are the pre-

dominant feature, a chorioretinal biopsy may be preferable. A technique has been described, where 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 is created that is large enough to allow the entrance of the vitreous cutter and suction tubing. With gentle cutting, several samples are obtained. Subretinal aspirates should be placed in a mild cytofixative, such as herpes-glutamic acid buffer-mediated organic solvent protection effect (HOPE) fixative or CytoLyt (Cytyc) [23].

Approximately 97% of VRL cases are diffuse large B-cell lymphoma (the remaining 3% are T-cell and other rarer forms) with characteristic histologic and cytologic features [24]. Cells are two to four times larger than normal lymphocytes and pleomorphic and have scant cytoplasm. The nuclei may be round, oval, or indented, with conspicuous nuclear membranes, occasional finger-like protrusions, and multiple, prominent, eccentrically located nucleoli (Fig. 7.4). Mitoses are frequently observed. With the use of electron microscopy, intranuclear inclusions, cytoplasmic crystalloids, and pseudopodal extensions of the cytoplasm, cytosomes, and autophagic vacuoles can be identified [25].

Due to limited cellularity, it can be difficult to reach a conclusive diagnosis based solely on cytopathologic findings. Ancillary techniques include immunohistochemistry, flow cytometry, gene rearrangement studies using the polymerase chain reaction (PCR), and determination of interleukin levels. Immunohistochemistry can be used to identify markers for leukocytes (CD45), B cells (CD20, CD79a, PAX-5), T cells (CD45RO), and macrophages (CD68) [26]. VRL frequently expresses MUM1/IRF4, BCL6, and BCL2 and typically lacks CD10 and plasma cell markers (such as Vs38c and CD138) [27]. The use of antibodies directed against κ and λ light chains can be used to establish clonality [28]. PCR-based tests are used to detect monoclonal proliferation of B lymphocytes, clonal heavy chain immunoglobulin gene rearrangement, bcl-2 gene translocation, and T-cell gene rearrangements. Flow cytometry provides a means to quantitatively assess the proportion of cells in a given sample that demonstrate these markers. An elevated ratio of interleukin-10 (IL-10) to interleukin-6 (IL-6) has been shown to be suggestive of VRL [29]. While helpful as supportive evidence for diagnosis, the interleukin ratio alone as a diagnostic tool is not clearly established, and cases with VRL with low interleukin ratios have also been reported [30]. Recently, MYD88 mutations have been shown to occur frequently in VRL, and their detection may improve the diagnostic yield of vitrectomy specimens [31].

Central Nervous System

Cranial 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. 7.5). Meningeal enhancement with gadolinium is indicative of meningeal involvement. CT scans of the chest, abdomen, and pelvis are performed 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 males over age 60 years because of frequent CNS involvement in testicular lymphoma.

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. Systemic nodal and/or visceral involvement is rare at the initial diagnosis but is not uncommon in the terminal stages.

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 considered a CNS disease and requires systemic

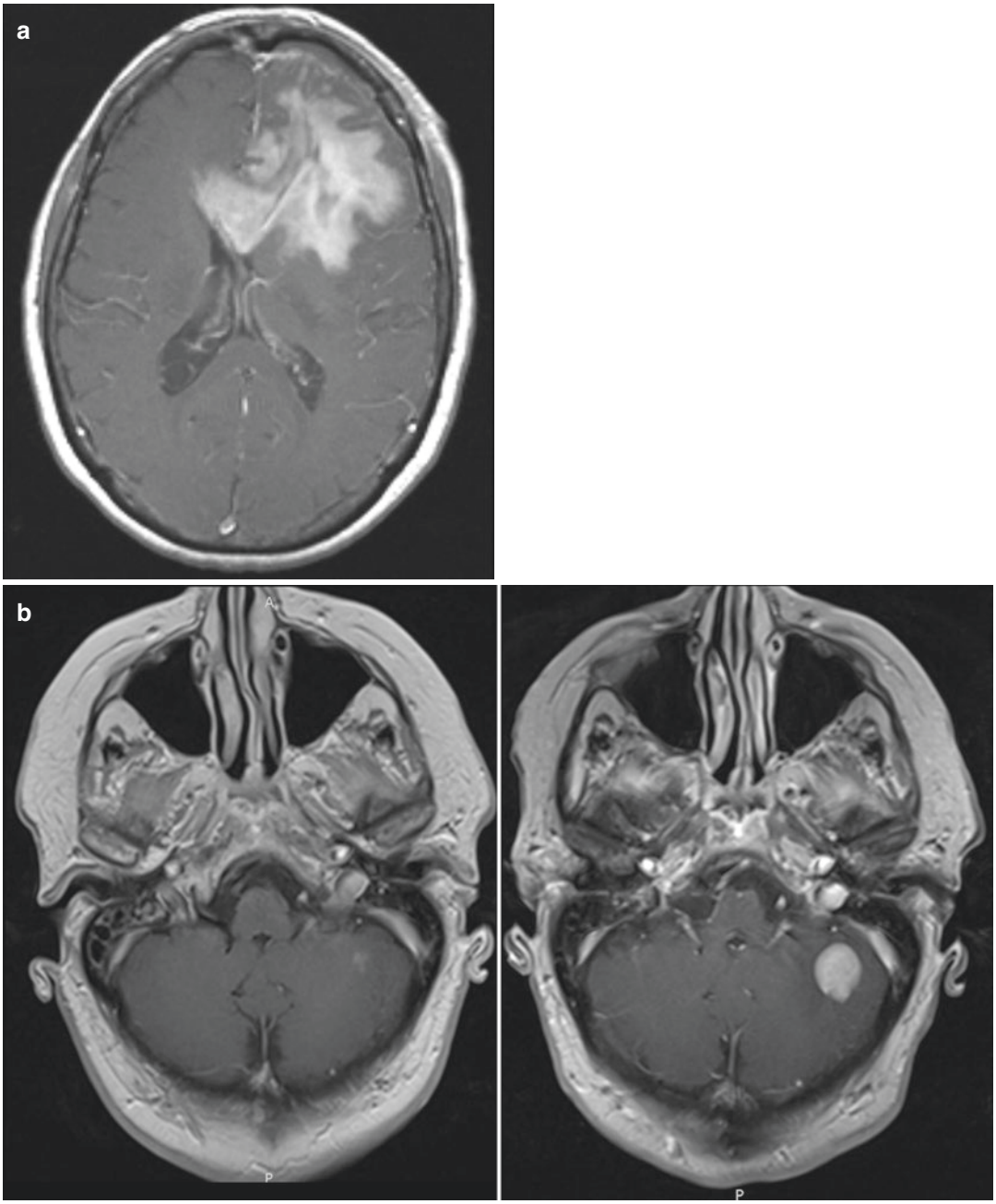

Fig. 7.5 T1-weighted MRI of the brain with gadolinium contrast, showing a diffusely enhancing area in the left frontal lobe (**a**) T1-weighted MRI at the time of diagnosis of VRL (left) and 4 weeks following session of oral steroids (right). There is obvious CNS involvement in the cerebellum which underscores the importance of steroid avoidance at the time of initial staging (**b**). (**a**: Reprinted from Singh et al. [32]. With permission from Elsevier)

therapy. Whipple's disease is a rare, multi-organ infection caused by the bacterium *Tropheryma whipplei*. Middle-aged Caucasian men in the United States and continental Europe are most frequently affected [33]. 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.

Vitreous amyloidosis can also mimic the clinical appearance of VRL (Fig. 7.6). This rare entity is usually observed in the setting of systemic amyloidosis, although localized ocular involvement can occur. Vitreous involvement appears to be linked to the hereditary neuropathies associated with mutation of amyloid protein transthyretin (TTR) [34]. 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. 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. 7.7). Retinal

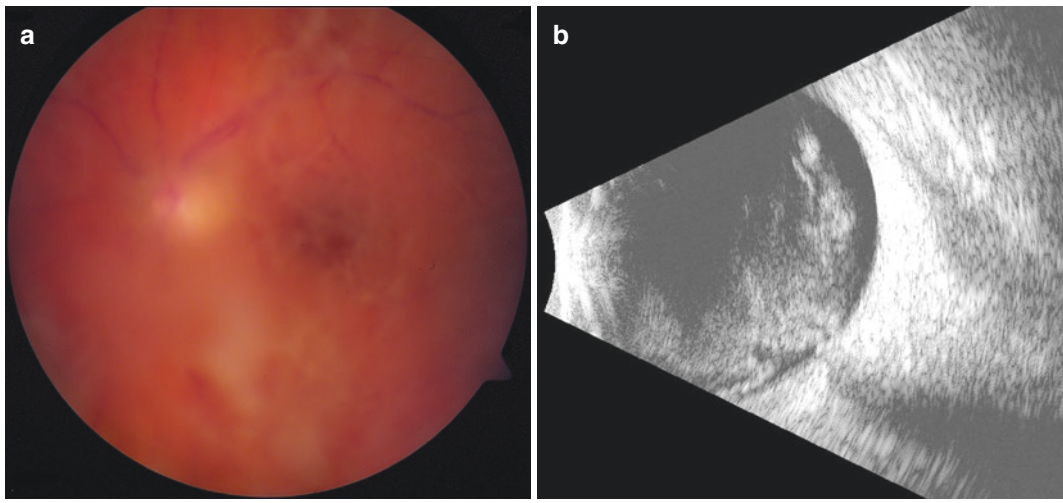

Fig. 7.6 Vitreous amyloidosis can mimic the clinical appearance of vitreoretinal lymphoma. The vitreous deposits are amorphous, predominantly in the posterior vitreous and overlying the posterior pole (**a**) and be observed as dense vitreous opacities on ultrasonography (**b**)

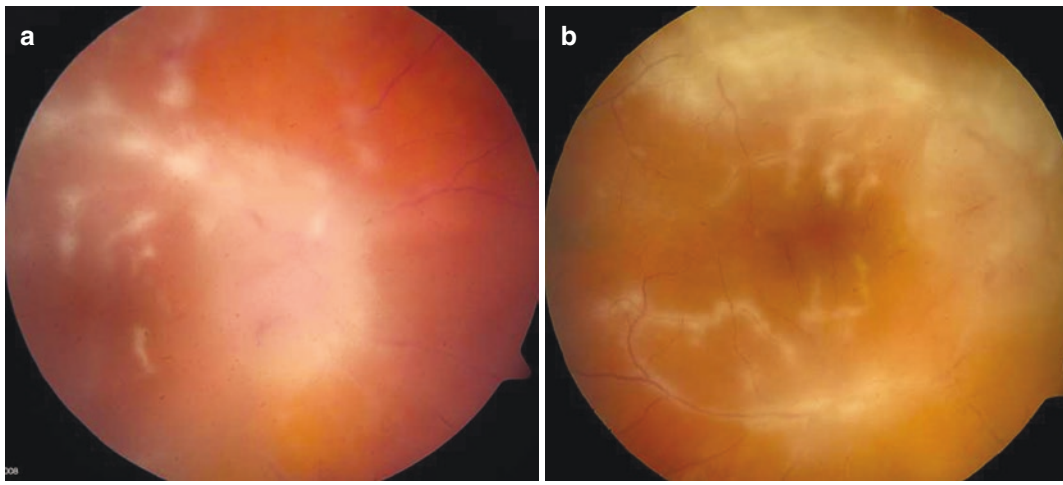

Fig. 7.7 The right optic disc, surrounding retina, and perivascular areas show inflammatory infiltrates in a patient with HTLV-1 retinitis (**a**). Following vitrectomy 6 weeks from initial photographs, the perivascular infiltrates are seen more distinctly (**b**). (Reprinted from Agarwal et al. [35]. With permission from Wolters Kluwer Health, Inc.)

biopsy with subsequent light microscopy evaluation, immunophenotypic studies, and PCR to detect clonal T-cell receptor gene rearrangement may be required for definitive diagnosis [36].

Choroidal tumors including metastasis and amelanotic melanoma can also mimic VRL. HIV infection predisposes to both opportunistic infections and VRL; 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 VRL should be differentiated from diffuse unilateral subacute neuroretinitis, birdshot retinochoroidopathy, multifocal choroiditis, multiple evanescent white-dot syndrome, and punctate inner choroidopathy. While intravascular lymphoma can occur, when perivascular infiltrates are present, conditions such as ocular sarcoidosis and retinal vascular disorders should be considered. Patients with systemic lymphoma, not arising in the CNS, develop choroidal rather than retinal infiltrates and are more likely to have a superimposed viral or fungal retinitis rather than an intraocular lymphoma.

Treatment

PCNSL is sensitive to corticosteroids; therefore, exposure to corticosteroids should be avoided in suspected cases until tissue diagnosis is confirmed. The treatment of PCNSL has evolved in recent years, and there is a general consensus that regimens containing high-dose methotrexate yield better response rates and outcomes than regimens that do not contain high-dose methotrexate. A schema outlining an approach of management is shown (Fig. 7.8).

Ophthalmic Treatment

Management of VRL should ideally be undertaken in partnership with an oncologist with expertise in lymphoma. As a high percentage of patients with VRL eventually develop CNS disease, some experts recommend that the treatment goal for VRL should be to eradicate 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. At present there is a lack of compelling evidence to suggest that ocular treatment prevents subsequent development of CNS disease.

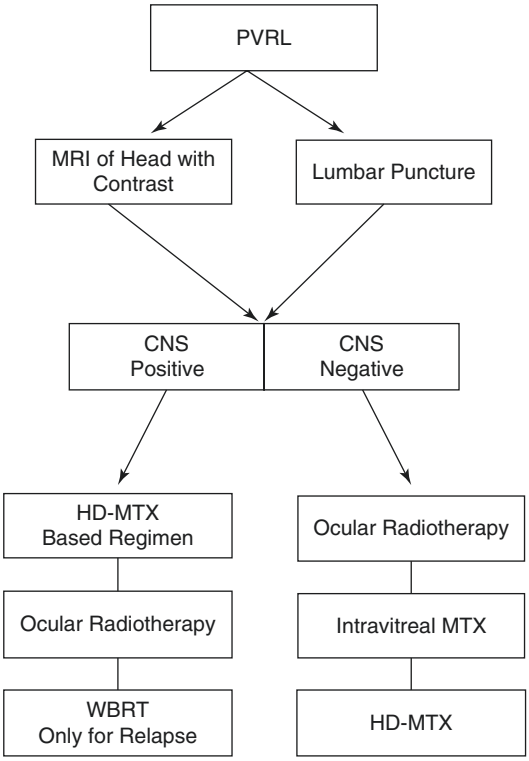

Fig. 7.8 Schema outlining our current approach of management of patients with VRL. HD-MTX, high-dose methotrexate; WBRT, whole-brain radiation therapy

Local Therapy for VRL

Options for local treatment for VRL include intravitreal delivery of therapy and ocular radiation. There has been no prospective, randomized clinical trial that has compared these two therapies directly. At present, most experts prefer intravitreal chemotherapy over ocular radiation as first-line therapy. Intravitreal methotrexate as primary therapy has been investigated with

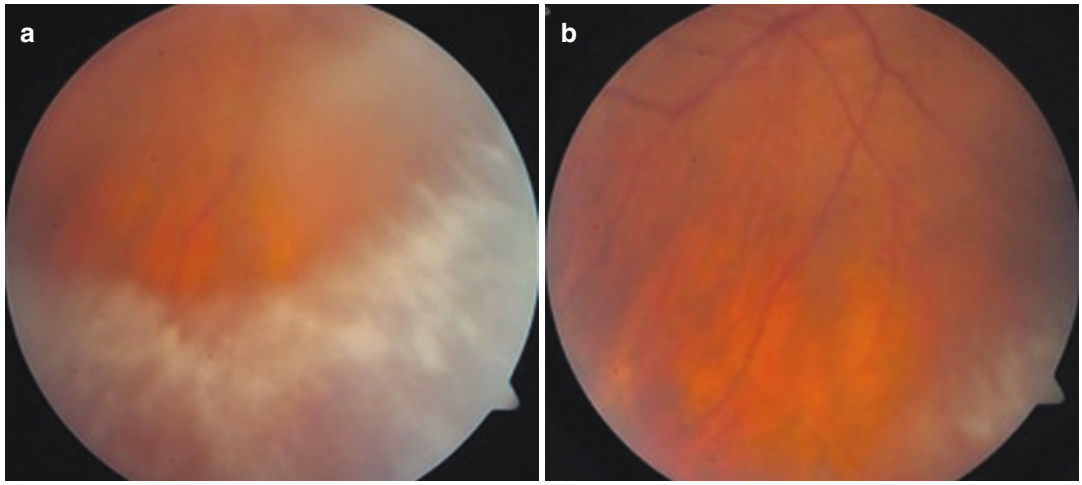

Fig. 7.9 Fundus appearance before (**a**) and after 3 months (induction and consolidation) of treatment with intravitreal methotrexate (**b**). Note dramatic clearance of vitreous cells

encouraging results (Fig. 7.9; Table 7.1). In one study, 44 eyes (26 patients) were treated with intravitreal methotrexate (400 μg/0.1 ml saline) administered according to an induction-consolidation-maintenance regimen given over the course of 1 year [37]. Clinical remission was achieved after a mean of 6.4 ± 3.4 (range, 2–16) injections of methotrexate, and 95% of eyes required less than 13 injections to reach a complete response [37]. While intravitreal methotrexate is fairly well tolerated, complications of therapy include corneal epitheliopathy, conjunctival hyperemia, increased intraocular pressure, cataract, maculopathy, and rarely vitreous hemorrhage [37]. Rare instances of hypotony have been observed. Intravitreal rituximab alone or used in combination with methotrexate has also shown encouraging results in smaller series. In one study, 48 eyes (34 patients) were treated with a median of 3.5 intravitreal injections of rituximab (1 mg/0.1 ml saline) for new diagnosis of VRL (68.8%), progressive disease (29.9%), and maintenance therapy (2.1%) [38]. Intravitreal rituximab ± methotrexate was the sole treatment in 19 (39.6%) of these eyes. A total of 31 eyes (64.6%) achieved a complete response (CR), following a median of 3 injections. Another 11 eyes (22.9%) achieved partial response (PR). Recurrent disease developed in 7 eyes [38]. Using a combination approach with intravitreal methotrexate and rituximab is attractive, as it may decrease the number of methotrexate injections and overall treatment-related side effects. More recently, there has been early evidence that low-dose intravitreal melphalan (10 μg /0.1 ml saline) may be suitable as first-line local therapy. In a small series of three eyes with cytologically confirmed VRL, a single intravitreal injection of melphalan achieved rapid tumor clearance from the vitreous in two eyes, and tumor control was achieved after six bimonthly injections in the third eye [39]. While further investigation is needed, intravitreal melphalan may be a reasonable treatment option and has the potential advantage of requiring fewer injections.

Prior to the use of intravitreal therapy, external beam radiotherapy (EBRT) was widely used as first-line treatment. Radiation remains an important option, particularly for patients with advanced bilateral involvement, for those who may not tolerate intravitreal chemotherapy, or for individuals who cannot return for multiple repeated injections. EBRT, or more recently intensity-modulated radiation therapy (IMRT), is delivered with a dose range of 30–50 Gy, divided into small (1.5–2.0 Gy) fractions [40]. While radiotherapy can achieve ocular control in the majority of cases, there is no evidence to suggest that its use prevents the development of CNS disease (Fig. 7.10). Due to the high incidence of bilateral disease, irradiation to both eyes should be considered for patients with biopsy-confirmed

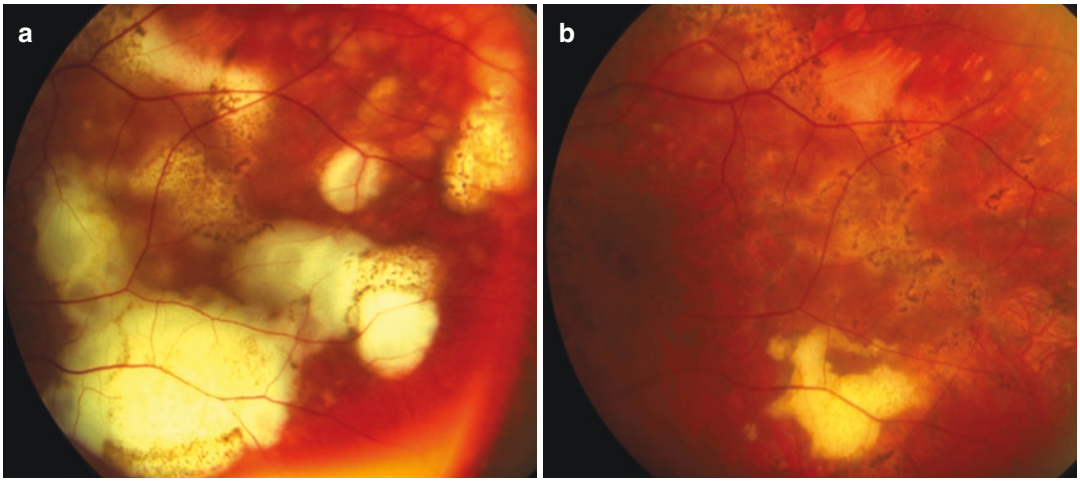

Fig. 7.10 Fundus photograph of the left eye demonstrating multiple creamy subretinal pigment epithelial deposits (**a**). Regression of the subretinal tumors following external beam radiotherapy at a total dose of 45 Gy (**b**). (Reprinted from Agarwal et al. [35]. With permission from Wolters Kluwer Health, Inc.)

VRL. As whole-brain radiotherapy (WBRT) may have significant side effects, its use for prophylaxis in patients without proven CNS involvement is not advisable. Lenalidomide may be a reasonable alternative to radiation for relapsed or refractory cases [41, 42].

Systemic Therapy for VRL and Risk of Subsequent CNS Disease

Disease relapse in the CNS is a major issue, particularly after local treatment with ocular radiotherapy or intravitreal chemotherapy. Systemic chemotherapy offers the potential advantage of simultaneous treatment of both ocular and microscopic intracranial diseases (Table 7.1). High-dose methotrexate is most commonly used in the treatment in PCNSL. Batchelor and colleagues reported their experience in nine patients with intraocular lymphoma treated with intravenous high-dose methotrexate at a concentration of 8 g/m^2 [43]. 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 CR in six and PR in one. Unlike PCNSL, experience with combination chemotherapy in VRL is extremely limited. Sandor and colleagues reported 100% response rate (11 CRs, 3 PRs) in 14 patients (5 with intraocular involvement) 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 observed, the duration was limited, and additional therapy was required due to relapse [44].

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. 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 [45].

In a report of 221 immunocompetent patients with PCNSL and/or VRL, Grimm and colleagues reported no difference in disease progression rates or overall survival in patients treated with local therapy versus those who received systemic therapies. This series, although the largest to date, was an uncontrolled, multicenter, and retrospective study that utilized different treatments depending on the preference of the treating physician [46]. It is possible that a combination of intravitreal and systemic chemotherapy may prolong the time to relapse [47].

A recent multicenter European study reported on outcomes of 78 patients treated at

17 centers based upon physician preference. Patients received ocular radiotherapy and/or ocular chemotherapy (31 patients), extensive systemic treatment (21 patients), and a combination of ocular and extensive systemic treatment (23 patients); 3 patients did not receive treatment. Extensive therapy included various combinations of systemic and intrathecal chemotherapy, whole-brain radiotherapy, and peripheral blood stem-cell transplantation. Overall, there was no difference at the rates of development of CNS disease (absent initially) between treatment groups (36% at a median follow-up of 49 months).

At the present time, there is a lack of compelling evidence that systemic chemotherapy will prevent the development of CNS disease. Moreover, its use has been associated with more severe adverse effects compared with local treatment [48]. An individualized patient-specific approach is generally recommended (Box 7.1).

Box 7.1 Salient features of Primary Central Nervous System Lymphoma

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

Central Nervous System

In the past, WBRT was the mainstay of treatment for PCNSL. This resulted in improvement in median survival to 12–18 months, compared to 4 months for untreated individuals [49]. In the 1990s, clinical trials using a combination of methotrexate-based chemotherapy and radiotherapy reported a further improved median survival of 40 months [49]. The combination of WBRT and chemotherapy is associated with a significant risk of neurotoxicity in older individuals (dementia); therefore chemotherapy alone is frequently selected over WBRT for individuals over age 60 years. More recently, reduced dose WBRT (23.4 Gy) has been combined with chemotherapy resulting in minimal neurotoxicity [50].

Gamma Knife radiosurgery (GKRS) has been studied in a prospective, observational cohort of 128 patients with histologically confirmed PCNSL. Patients were treated with either methotrexate (dose of 8 g/m^2) alone (control, 73 patients), or they received methotrexate plus GKRS (dose of 11–16 Gy, median 11 Gy) (55 patients). After a follow-up period of 24–49 months (mean, 36.9 months), the median survival rate from initial diagnosis was 26.8 months in the chemotherapy group and 47.6 in the chemotherapy, plus GKRS, group (p-value, 0.0034). All lesions treated with GKRS demonstrated a complete response based on MRI 3–8 weeks (mean range, 6.3 weeks) following therapy [51].

As the blood-brain barrier restricts drug entry into the CNS, various strategies to overcome this have been evaluated. These include the use of high-dose chemotherapy, intrathecal drug delivery, intraventricular drug delivery by a reservoir, and temporary disruption of the blood-brain barrier (BBBD) with mannitol infusion [49]. In a large multi-institutional experience of 149 newly diagnosed PCNSL patients (with no prior WBRT) who 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 progression-free survival and overall survival of 1.8 and 3.1 years, respectively [52]. Maculopathy is an

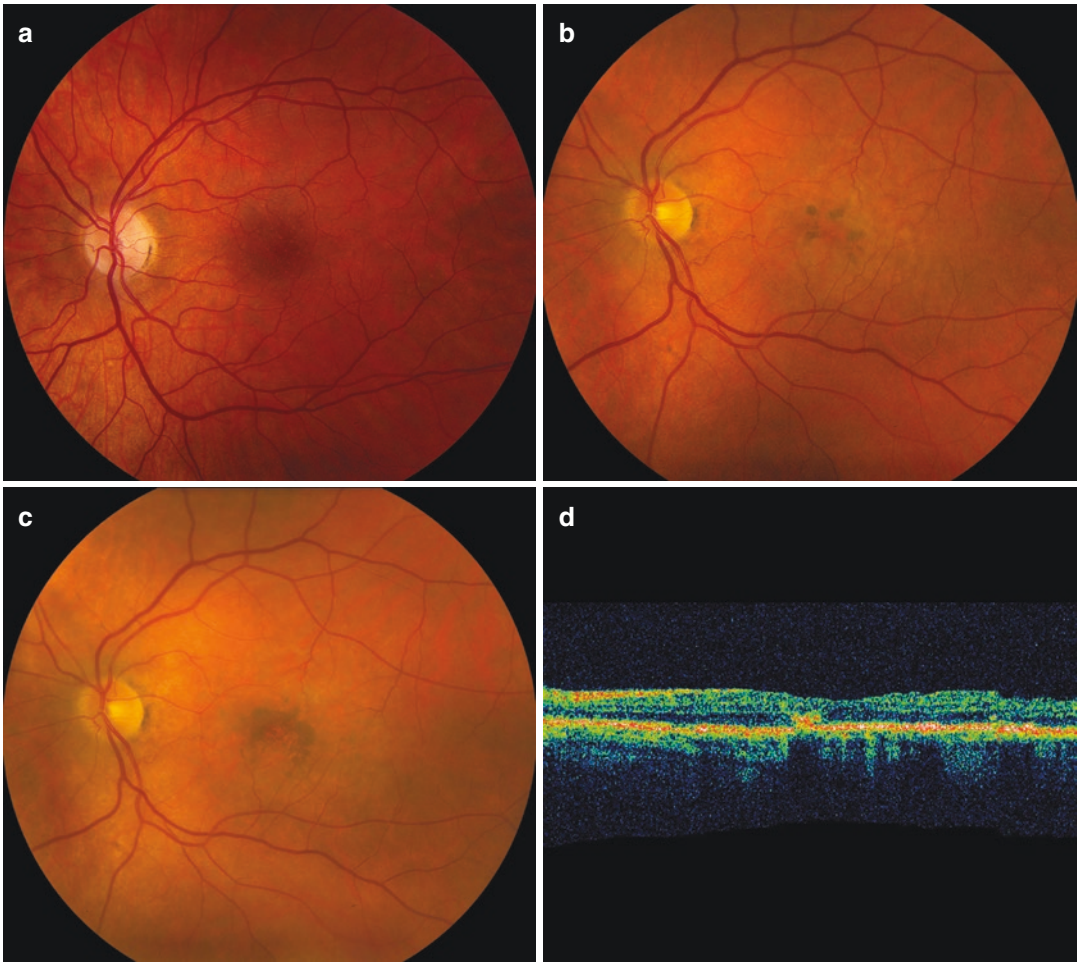

Fig. 7.11 Color photographs of left fundus from two patients with primary central nervous system lymphoma treated with blood-brain barrier disruption therapy demonstrating the spectrum of hyperpigmentation and retinal pigment epithelium (RPE) loss within the macula. Mild and moderate severity (**a**). Second patient 4 months after completion of treatment (**b**). Note progression of retinal pigment epithelium changes (**c**). Optical coherence tomography showing irregular thickening of the retinal pigment epithelium (**d**). (Reprinted from Galor et al. [53]. With permission from Elsevier)

ocular complication associated with BBBD with mannitol (Fig. 7.11). 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 an 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 decision to use WBRT and its timing and dose are still unclear, given the significant risks of late neurotoxic effects. Further evaluation is needed to investigate the role of radiation in upfront treatment of PCNSL.

For recurrent or refractory PCNSL, small molecules have recently been investigated. Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, has been studied at doses of 560 mg and 840 mg daily. In the 560 mg trial, 52 patients with recurrent PCNSL or ocular lymphoma were enrolled

in a French study, and the overall response rate (ORR) was 50% after two cycles of ibrutinib [54]. In the 840 mg trial, 20 patients with recurrent PCNSL and secondary CNS lymphoma achieved an ORR of 75% [55]. Immune checkpoint inhibitors have also recently been investigated. In a recent series of five patients (four with relapsed/refractory PCNSL and one with CNS relapse of primary testicular lymphoma), the anti-PD1 antibody nivolumab resulted in a 100% clinical and radiographic response. Of these, three patients had progression-free survival at 13–17 months which suggested that nivolumab may be useful in the treatment of relapsed/refractory PCNSL [56]. This initial small study resulted in a subsequent multicenter trial to investigate single-agent nivolumab in PCNSL and testicular lymphoma (NCT02857426). In addition, a single-institution trial with pembrolizumab (NCT02779101) is ongoing to investigate the role of PD-1 blockade in PCNSL.

Prognosis

Survival of patients with PCNSL following WBRT is poor, ranging from 12 to 18 months, but may increase following high-dose methotrexate-based chemotherapy alone or when used in combination with radiation [57]. Age less than 60 years at diagnosis and high initial performance status are well-recognized favorable prognostic factors in PCNSL. The International Extranodal Lymphoma Study Group has devised a prognostic scoring system utilizing five variables associated with poor prognosis: 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) [58]. Involvement of the brain stem and leptomeninges also portend an unfavorable prognosis. The presence or absence of vitreoretinal involvement in the setting of existing CNS disease does not appear to be a prognostic factor that influences overall survival.

Summary

Primary central nervous system lymphoma (PCNSL) is a variant of extra-nodal non-Hodgkin's lymphoma (NHL), a high-grade malignancy predominantly of B-cell origin. There are no known risk factors in immunocompetent individuals; however, congenital immunodeficiency and iatrogenic and acquired immunosuppression (HIV/AIDS) are risk factors for PCNSL. The brain, spinal cord, leptomeninges, and eyes, either separately or in combination, can be involved. Patients may be asymptomatic, but up to 50% present with painless blurred vision, floaters, or both. The hallmark diagnostic features are vitreous cells and subretinal pigment epithelial infiltrates. Diagnostic techniques including vitreous, retinal, and subretinal biopsy are needed to establish diagnosis in most cases. There is a general consensus that regimens containing high-dose methotrexate (at least 3.5 G/m^2), with or without WBRT, yield better response rates than regimens that do not contain high-dose methotrexate. Disease relapse in the CNS is a major issue, particularly after local treatment with intravitreal therapy and/or radiation. Management should ideally be undertaken in partnership with an oncologist with expertise in lymphoma.

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