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Current Concepts in Diagnosing and Managing Primary Vitreoretinal (Intraocular) Lymphoma

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Abstract

Primary vitreoretinal lymphoma (PVRL), previously called primary intraocular lymphoma (PIOL), is a rare and fatal ocular malignancy. PVRL is a subset of primary central nervous system lymphoma (PCNSL), mostly a diffuse large B-cell lymphoma. The diagnosis of PVRL is often challenging as it often masquerades as chronic uveitis. PVRL requires invasive procedures for tissue diagnosis. Cytology/pathology, molecular pathology (immunoglobulin or T-cell receptor gene rearrangement), immunohistochemistry, biophysical technology (flow cytometry), and cytokine analysis (interleukine-10) are often required. The therapies that have been successful in systemic lymphomas have not been reliably effective in PVRL and PCNSL. Current management of PVRL involves aggressive chemotherapy (methotrexate and rituximab) and radiation therapy. PVRL normally responds well to initial treatment; however, relapse rate and CNS involvement are high, resulting in poor prognosis and limited survival. A professional team of medical experts in ophthalmology, oncology (particularly neuro-oncology), and pathology is essential for optimizing patient management.

Terminology

In a clinico-pathological survey of 618 lymphoma cases that was published in 1942, Gallo and Mallory documented a “stem cell lymphoma,” a histological subclass of “reticulum cell sarcoma” originated from the eyelid (Gallo and Mallory, 1942). They described the cells of this lymphoma with large nuclei and prominent densely staining nucleoli. In 1966, Rappaport classified lymphoma into three groups based on cellular morphology: Hodgkin’s disease, lymphosarcoma, and reticulum cell sarcoma (Rappaport, 1966). Although a few cases of intraocular “reticulum cell sarcoma” were reported in the 1950s and early 1960s, these handful of cases did not demonstrate lymphoma cells in the retina, vitreous, optic nerve, and/or central nerve system. In 1968, Vogel and associates presented 4 histological cases of “reticulum cell sarcoma” invading the retina (Vogel *et al*., 1968). Later, an unusual link was found between this intraocular lymphoma and primary central nervous system lymphoma (PCNSL) (Qualman *et al*., 1983; Char *et al*., 1981).

In the late 1970s and early 1980s the term “reticulum cell sarcoma” became a misnomer as researchers demonstrated the origin of the tumor cells to be transformed lymphoid cells (malignant B- and T- lymphocytes), not histiocytes. In 1982, the National Cancer Institute, National Institutes of Health sponsored a study of classification of non-Hodgkin’s lymphoma and replaced the Rappaport classification. With the advancement of immunology

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and genetics, the characterization and algorithm of lymphomas have been taken over by the World Health Organization (WHO) Lymphoma Classification. The “reticulum cell sarcoma in the eye” was changed to “primary intraocular lymphoma” (Char *et al.*, 1988b). Primary intraocular lymphoma was defined as “isolated eye tumor” or “tumor that involves both the globe and the CNS” (Char *et al.*, 1988b). The WHO classification emphasizes an approach whereby the clinical features are correlated with distinct morphology, immunophenotype, and genotype of each neoplasm. The term “primary intraocular lymphomas” should represent lymphomas originating from all ocular tissues. Since lymphomas originating from the retina/vitreous and the choroid are distinctive, “primary vitreoretinal lymphoma (PVRL)” is proposed and used (Coupland *et al.*, 2009).

Diagnosis

PVRL is a rare extranodal non-Hodgkin’s lymphoma that originally invades intraocular tissues: the retina, vitreous, and/or optic nerve (Chan and Gonzalez, 2007; Chan *et al.*, 2011). PVRL is the most common intraocular lymphoma, usually of the B-cell type as diffuse large B-cell lymphoma. Infrequently, there is PVRL of T-cell type. PVRL is closely related to PCNSL (Petersson *et al.*, 1998). In the U.S., it is estimated that there are 300–380 new cases of PVRL per year (Chan *et al.*, 2011). Approximately 80% of PVRL patients eventually develop PCNSL and approximately 20% of PCNSL patients present with PVRL (Coupland *et al.*, 2004; Hochberg and Miller, 1988; Hong *et al.*, 2011; Nasir and DeAngelis, 2000; Surawicz *et al.*, 1999). Consequently, PVRL is often fatal because of ultimate CNS association (Chan *et al.*, 2011; Hormigo *et al.*, 2004; Peterson *et al.*, 1993). When treated with conventional therapy, relapsing PCNSL had a poor prognosis with a one-year overall survival of 25–40% (Sierra del Rio *et al.*, 2009). The mean survival of PVRL is 32 months and 5 year survival rate is 61% in Japan (Kimura *et al.*, 2012). PVRL differs from the metastatic lymphoma in the eye, which often locates in the choroid of generally sick patients with known systemic lymphoma (Chan and Gonzalez, 2007). Bilateral ocular involvement is common.

PVRL is a masquerade syndrome that mimics chronic uveitis, which creates difficulty in diagnosis (Chan *et al.*, 2011; Davis, 2013; Faia and Chan, 2009; Kinoshita *et al.*, 2012; Mochizuki and Singh, 2009). The diagnosis of PVRL requires a clinical suspicion and more importantly, the tissue diagnosis and confirmation (Chan, 2003). Among the earliest true PVRL cases published in 1968 (Vogel *et al.*, 1968), a 67-year-old male patient had clinical diagnosis of uveitis and the pathology showed lymphoma cells not only in his retina and uvea, but also in his brain. In another case, a 71-year-old female patient presented clinically with pericorneal injection of a steamy cornea and blindness in the right eye. Her enucleated right eye showed massive chronic inflammation in the anterior segments and vitreous; significantly, large atypical lymphoid cells were found in the thickened retina (Vogel *et al.*, 1968). Since then, many similar cases that were first misdiagnosed as “uveitis” and later found to have lymphoma cells in the retina, vitreous, and brain have been reported in the literature (Davis, 2013; Sen *et al.*, 2009).

Clinically, PVRL typically occurs in older patients with median age range of 60s (Chan *et al.*, 2011; Mochizuki and Singh, 2009; Whitcup *et al.*, 1993). In general PVRL patients do not have systemic symptoms such as cachexia, fever, and lymphadenopathy (Chan and Gonzalez, 2007; Hormigo and DeAngelis, 2003). If there is no CNS involvement, these patients usually complain of blurred vision and floaters (Chan *et al.*, 2011; Davis, 2013; Mochizuki and Singh, 2009). Patients with CNS involvement can present with neurological symptoms depending on the tumor location in the brain. Since the frontal lobe is the most frequent location for PCNSL, the common presenting symptom is personality change (Mochizuki and Singh, 2009).

Most PVRL cases have little anterior segment inflammation and the eye is usually quiet and white (Chan *et al.*, 2011). Slit lamp examination may show mild inflammation but it is non-specific. Dilated fundus examination is essential for the clinical diagnosis. Vitreous cells and haze are often striking (Faia and Chan, 2009). The cells can be in clumps or in sheets (Figure 1). In a series of 32 patients, Freeman *et al.* (1987) reported 50% presented with vitreous cells. Char *et al.* (1988a) reported 100% vitreous cells in their study of 20 patients. We and others also reported vitreous cells as the most common ocular finding (Chan, 2003; 2011; Hong *et al.*, 2011; Levy-Clarke *et al.*, 2005; Sen *et al.*, 2009; Whitcup *et al.*, 1993). Frequently, the cells (lymphoma cells mixed with reactive inflammatory cells) in the vitreous are abundant, but visual acuity can be unexpectedly good, or at least better than expected (Whitcup *et al.*, 1993). Retinal and subretinal lesions are classically creamy, white to orange infiltrates (Figure 2). They may have feathery or distinct borders, may be single isolated or multiple confluents, and can be located in the sub-retinal pigment epithelial (RPE), sub-retinal, and/or intra-retinal regions.

Since the PVRL cells tend to deposit in the sub-RPE, above the Bruch's membrane first (Chan *et al.*, 2003), various ocular images can illustrate different characteristic patterns (Chan *et al.*, 2011; Chan and Sauer, 2009). Fundus autofluorescence in 5 eyes with PVRL showed bright hyperfluorescent spots corresponding to the sub-RPE infiltrates, and hypofluorescent areas corresponding to RPE atrophy where, presumably, tumor cells were previously resided (Ishida *et al.*, 2010). Fundus fluorescein angiogram (FA) illustrates RPE disturbances as granular, mottling, and late staining patterns (Cassoux *et al.*, 2000; Fardeau *et al.*, 2009; Velez *et al.*, 2002). Clusters of round, hyper- or hypo-fluorescent spots reflect RPE abnormalities. Ocular coherence tomography (OCT) shows nodular hyperreflective lesions at the RPE level. In an imaging study of 53 patients with PVRL, the positive predictive value of imaging with OCT, FA, or indocyanine green angiography (ICG) was 88.9% and the negative predictive value was 85%, the odds ratio was 45.22 (Fardeau *et al.*, 2009).

Because PVRL is closely related to PCNSL, it is imperative to evaluate the CNS with contrast-enhanced magnetic resonance imaging (MRI) (Chan *et al.*, 2011; Sen *et al.*, 2009). Patients with PCNSL have either single or multiple lesions with discrete or diffuse borders. Cerebrospinal fluid (CSF) evaluation is highly recommended despite a low yield for lymphoma cells in the CSF (Chan *et al.*, 2002). However, demonstration of lymphoma cells in the CSF supports the diagnosis of PVRL and spares the patient from further invasive diagnostic procedures such as diagnostic vitrectomy or retinal biopsy.

The gold standard for diagnosing PVRL requires the detection of malignant lymphoid cells in the retina, vitreous, and/or the optic nerve (Coupland *et al.*, 2004; Rajagopal and Harbour, 2011; Sen *et al.*, 2009; Zaldivar *et al.*, 2004). Surgical removal of ocular fluids (aqueous aspiration and/or diagnostic vitrectomy), retinal or chorioretinal biopsy, and rarely diagnostic enucleation are performed. Since PVRL cells rapidly die once they leave the eye, it is critical to process the specimen promptly (Chan, 2003). Routine cytology and histopathology are used to identify PVRL cells, which are characterized with large irregular nuclei, prominent nucleoli, and scanty basophilic cytoplasm (Figure 3). Mitoses are variable. Reactive lymphocytes are often mixed with PVRL cells and the PVRL cells are easily necrotic and degenerated, which can create difficulty in recognition of the PVRL cells.

Immunohistochemistry or flow cytometry demonstrates the monoclonality, either B-cell (kappa or lambda light chain) or T-cell type for the lymphoma cells (Davis *et al.*, 1992; 1997). Flow cytometry is an effective tool and can provide accurate information for the diagnosis (Davis *et al.*, 1997). Molecular analysis of the PVRL cells detects either *IgH* gene rearrangements in B-cell lymphoma or *T-cell receptor* gene rearrangements in T-cell

lymphoma. In a large series of 114 PVRL cases, the diagnostic efficiency of molecular techniques was 99.5% using microdissection by selecting a minimum of 15 atypical lymphoid cells from the specimen combined with polymerase chain reaction (Wang *et al.*, 2011). Without microdissection, molecular testing may be less sensitive and specific (White *et al.*, 1999).

B-cell lymphoma produces ample interleukin-10 (IL-10) and normal inflammatory cells (macrophages and lymphocytes) secrete more IL-6. In 1995, high levels of vitreous IL-10 were first reported in three B-cell PVRL patients (Chan *et al.*, 1995); since then other publications have confirmed the elevation of IL-10 in ocular fluids of patients with PVRL (Cassoux *et al.*, 2007; 2001; Whitcup *et al.*, 1997). Currently, a high IL-10 and/or a ratio of IL-10:IL-6 greater than 1 in aqueous and/or vitreous have become adjunctive and supportive biomarkers for the diagnosis of PVRL, particularly the B-cell PVRL (Asencio-Duran *et al.*, 2012; Chan *et al.*, 2011; Davis, 2013; Kimura *et al.*, 2012; Rajagopal and Harbour, 2011; Sen *et al.*, 2009; Sugita *et al.*, 2009). Additionally, IL-10 (−1082) G↔A polymorphism is recently found to be associated with PVRL and PCNSL (Ramkumar *et al.*, 2012). This association is a risk factor for higher ocular IL-10 levels and correlates with more aggressive malignancy.

Clinical manifestation, imaging findings (eye and CNS), flow cytometry, ocular IL-10 levels, and molecular data are helpful adjuncts for correct diagnosis, although the diagnosis of PVRL relies on the identification of lymphoma cells in the retina, vitreous, and/or optic nerve.

Treatment

Currently there is no standard optimal therapy for PVRL due to its rarity. Even though PVRL cells are highly radiosensitive and chemosensitive (e.g., methotrexate), the overall survival rate is still quite low. In 2011, the International PCNSL Collaborative Group organized a symposium on PVRL and recommended the following therapeutic principles: systemic treatment if disease involves the CNS; local treatment (the eye) if the disease involves only the eye with close follow-up and ongoing collaboration between neurooncologists and ophthalmologists (Chan *et al.*, 2011). It is crucial to have a team of ophthalmologist, oncologist (neuro-oncologist or hemato-oncologist), and pathologist for the management of each PVRL patient.

The recommendations of the therapeutic regimens for the PVRL without CNS involvement are: for PVRL that is limited to one eye, local ocular treatment with intravitreal methotrexate, intravitreal rituximab, or ocular radiation with 30–35 Gy external beam; for PVRL involving both eyes, the recommendations were mixed, with preferable local therapy combined with systemic treatment. In other words, systemic chemotherapy has been suggested in addition to intravitreal medications for bilateral PVRL (Chan *et al.*, 2011; Pe'er *et al.*, 2009). For patients with coexisting PVRL and PCNSL, a high-dose methotrexate based systemic therapy, possibly with systemic rituximab, was proposed in conjunction with local ocular therapy, especially given the limited penetration of systemic agents into the vitreous cavity. There was consideration of whole brain radiotherapy in conjunction with ocular radiotherapy in those who had failed systemic chemotherapy and were too debilitated or did not meet criteria for more aggressive therapy such as autologous stem cell transplantation (ASCT) (Chan *et al.*, 2011). However, some neurooncologists might not include local treatment to the eyes if there was concurrent ocular and CNS lymphoma (Lisa DeAngelis, personal communication).

A recent review on current care of PCNSL discussed whole brain radiation with 20–50 Gy combined with or without chemotherapy (methotrexate, rituximab, or blood-brain barrier

disruption) (Rosenfeld and Pruitt, 2012). Less than 5% of patients had associated systemic lymphoma. Whole brain radiation given with or without chemotherapy often induced a delayed neurotoxicity with decline in cognitive function, ataxia, urinary incontinence, dementia, and even death (Rosenfeld and Pruitt, 2012). Now more neuro-oncologists are avoiding initial radiation therapy and administering chemotherapy first, then consolidating with a lower dose of whole brain radiation (23 Gy) only after failure of systemic chemotherapy (Tracy Batchelor, personal communication). Another recent review of a comparison between chemotherapy alone or a combined modality therapy with high-dose methotrexate and whole brain radiotherapy for PCNSL in immunocompetent patients found that the combined modality had better response rates but higher neurotoxicity (Prica *et al.*, 2012). The findings support that the preferred strategy is chemotherapy alone for older PCNSL patients.

For the relapsed or refractory PCNSL and PVRL, intense chemotherapy of thiotepa, busulfan, and cyclophosphamide, combined with hematopoietic stem cell rescue were used in 79 patients who did not respond to high-dose methotrexate (Soussain *et al.*, 2012). The patients were followed for 56 months. The 5-year overall survival probability was 62% compared to the 51% probability in the general PCNSL population, and the 5-year event free survival probability was 43.7% compared to the 37.8% in the general PCNSL population. Although no firm conclusions can be made from this study, prospective multicenter randomized studies (NCT00863460 and NCT01011920) are underway.

Currently there are two National Cancer Institute (NCI) sponsored, open randomized clinical trials to address the following questions: (1) high dose chemotherapy/autotransplant versus standard chemotherapy for consolidation: “Combination chemotherapy with or without autologous stem cell transplant in treating patients with CNS B-cell lymphoma (CALGB 51101 - P.I.: Tracy Batchelor)” and (2) chemotherapy and low dose whole brain radiation therapy as consolidation: “Rituximab, methotrexate, vincristine sulfate, procarbazine hydrochloride, and cytarabine with or without radiation therapy in treating patients with PCNSL (GTOG 1114 - P.I.: Antonio Omuro) (http://clinicaltrials.gov/).

In summary, neuro-oncologists and ophthalmologists must consult one another and manage their PCNSL/PVRL patients with a team approach. Methotrexate-based polychemotherapy is recommended as the first line treatment. Combined radiation and chemotherapy exposes patients, especially elderly patients, to severe delayed neurotoxic effects. Intense chemotherapy with autologous stem-cell transplantation may become an effective salvage treatment for refractory and relapsed PCNSL (Chan *et al.*, 2011; Ricard *et al.*, 2012; Davis, 2013).

Conclusion

PVRL, a subset of PCNSL often masquerades as intraocular inflammation or uveitis; therefore the disease is easily misdiagnosed, resulting in inappropriate management and high morbidity and mortality. Ocular cytokine levels and molecular analyses can provide useful supplementary data for the diagnosis. Optimal therapy for PVRL becomes a great challenge to both the oncologist and ophthalmologist. Studying the cellular and molecular biology, epidemiology, pathology, physiology, immunology, and genetics of PVRL can make a considerable difference in the diagnosis, management, and prognosis of this devastating disease.

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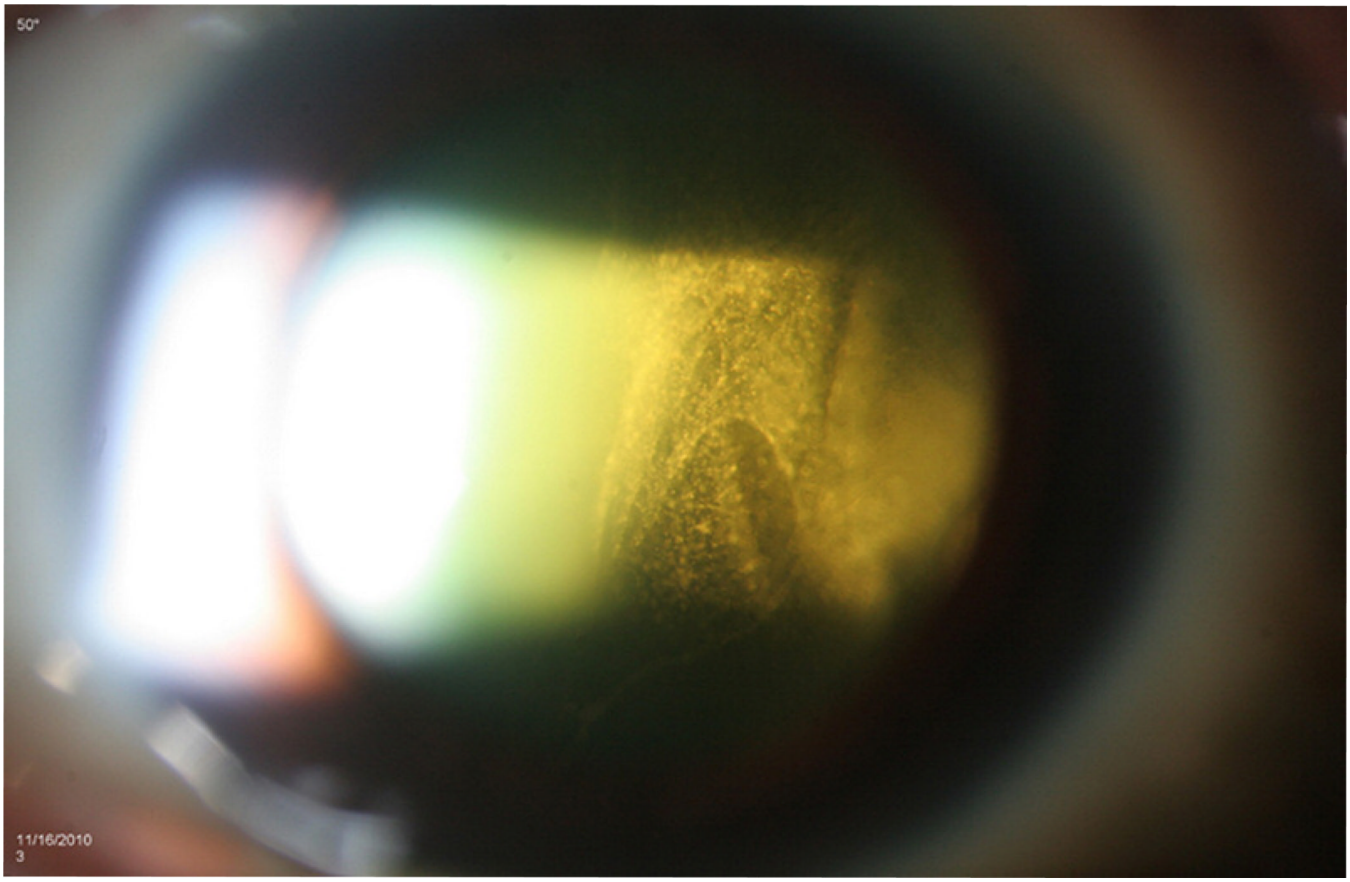

Figure 1.
Slit lamp biomicroscopy shows intense vitreous cells seen in sheets of a 62 year-old female patient with PCNSL/PVRL.

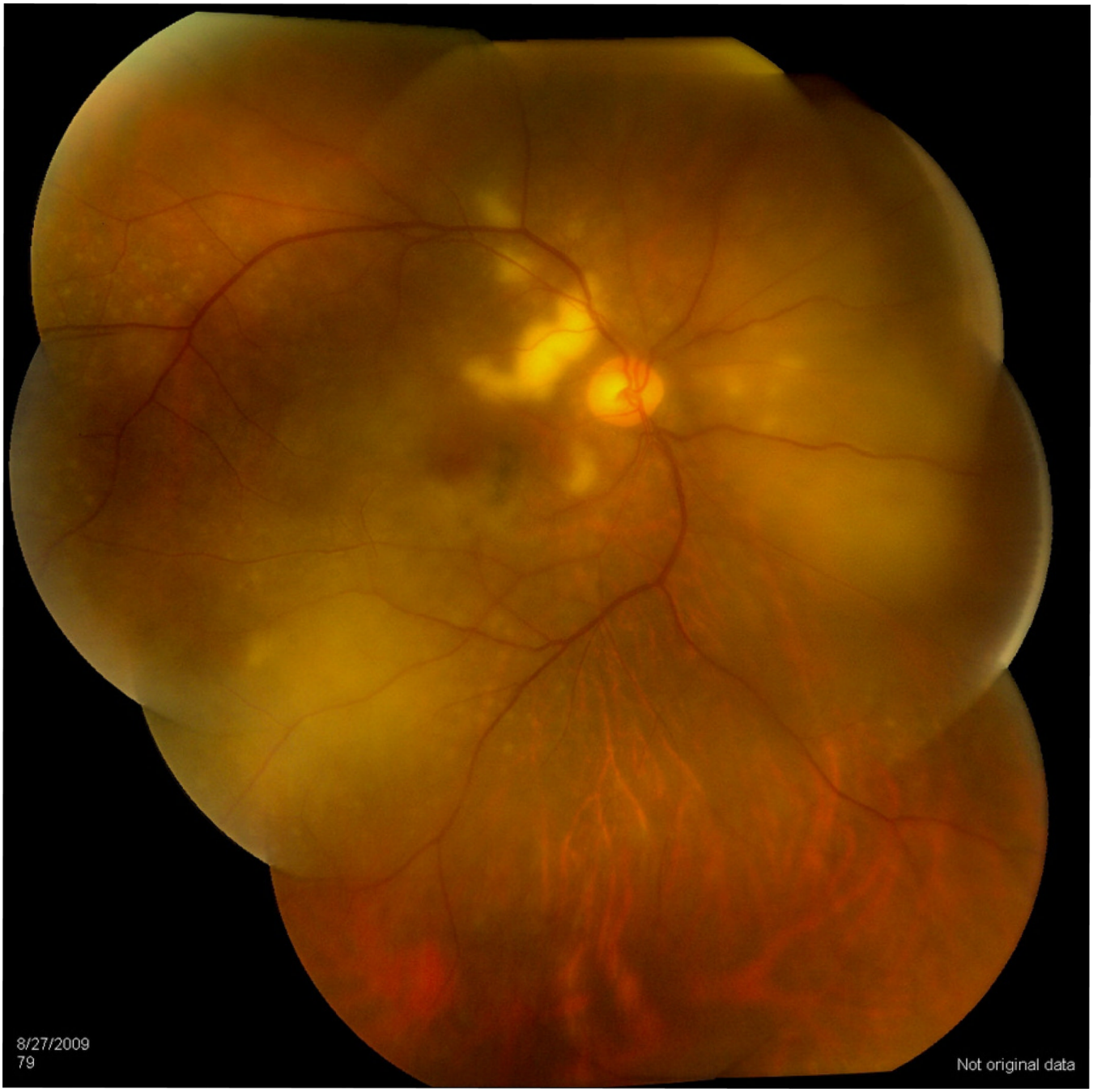

Figure 2.
Fundoscopy shows elevated yellowish subretinal lesions along the superior arcade and diffuse yellowish infiltrate in the inferonasal retina of a 59 year-old female with PCNSL/PVRL who presented as panuveitis initially.

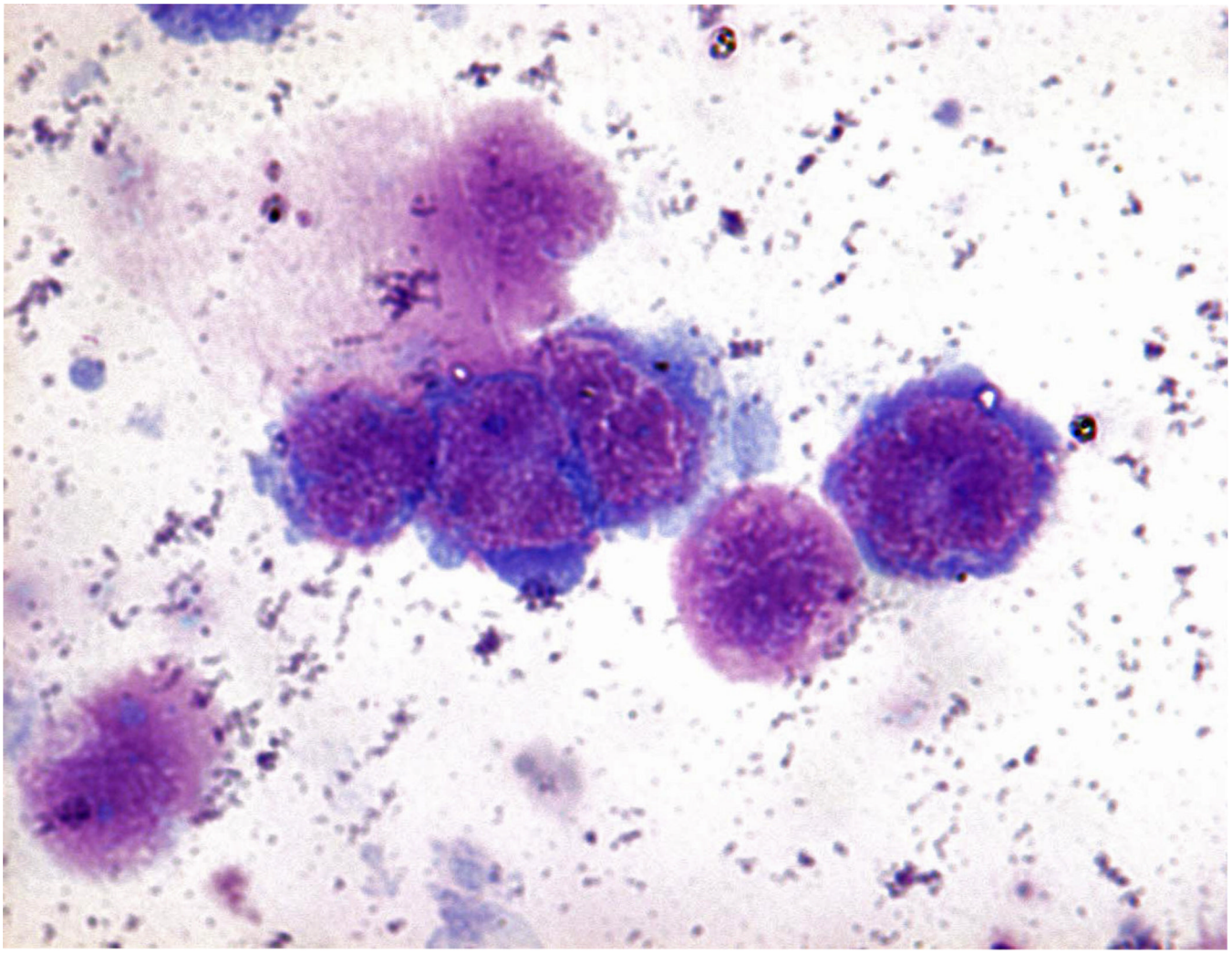

Figure 3.
Cytology of a vitreous specimen from a patient with PVRL showing large lymphoma cells with large irregular nuclei, prominent nucleoli and scanty basophilic cytoplasm. (Giemsa stain, original magnification ×400).