Update on Diagnosis and Treatment of Primary Vitreoretinal Lymphoma

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Xiao Zhang and Meifen Zhang

19.1 Introduction

Primary vitreoretinal lymphoma (PVRL) is one manifestation of primary central nervous system lymphoma (PCNSL) and typically a systemic disease. It often masquerades as chronic uveitis, especially posterior and pan-uveitis, and is frequently misdiagnosed at first. The golden standard for diagnosis is malignant lymphoid cells from the eye. Cytology and immunohistochemistry could confirm the diagnosis of PVRL. Flow cytometry, gene rearrangement, and intraocular cytokine detection are important auxiliary examinations. New methods using microRNA, gene mutation, and SNP might be helpful in the diagnosis and treatment response monitoring. Treatments of PVRL include systemic and local therapy. Intravitreal methotrexate and ocular radiotherapy are used for PVRL patients without brain involvement. Intravitreal anti-CD20 agent is a relatively new therapy, and seems to be safe and effective.

In 1953, Givner reported a patient with uveitis and died as a result of a malignant lymphoma of the brain [1]. Subsequently, ophthalmologists recognized the disease as intraocular large-cell lymphoma, or reticulum cell sarcoma. Since lymphomas are considered originating from the retina and vitreous body, PVRL is now used, but it is also known as primary intraocular lymphoma (PIOL). PVRL is a rare type of PCNSL, but is the most common lymphoma of the eye [2, 3]. Most patients are older than 50 years old, with median age range of 60s. Approximately 15–25% of patients with PCNSL have or will have ocular involvement. Conversely, 56–90% of patients with PVRL ultimately develop CNS disease [3]. The prognosis of PVRL is poor due to its close relationship with PCNSL.

X. Zhang · M. Zhang (✉)
Department of Ophthalmology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

19.2 Ocular Features

PVRL usually masquerades as chronic posterior or pan-uveitis, but it is unresponsive to corticosteroids or initially responsive to the therapy [4, 5]. In a retrospective review of 853 patients seen at the National Eye Institute Uveitis Clinic, 21 (2.5%) were diagnosed with neoplastic masquerade syndromes [6]. Common symptoms of PVRL at presentation are decreased visual acuity, blurred vision, and floaters. Most patients have bilateral lesions, but some of them may present symptoms unilaterally. Anterior segment inflammation is not obvious in most PVRL cases. There may be nonspecific manifestations such as different types of keratic precipitates and anterior chamber cells [4, 5, 7].

Vitreous cells and haze are typical signs of PVRL, often striking. As the most common ocular finding, vitreous cells may form clumps, sheets, or strands (Fig. 19.1a). Another typical sign is multifocal creamy infiltrative lesions in the deep retina [4, 5, 7]. These lesions may be located in the subretina, intraretinal, and subretinal pigment epithelial (RPE) regions. They can have distinct borders, as well as feathery borders (Fig. 19.1b). In advanced cases, exudative retinal detachment may be presented (Fig. 19.1c). RPE atrophy with or without subretinal fibrosis was left after treatment (Fig. 19.1d).

19.3 Diagnose Methods

19.3.1 Ocular Biopsy

The golden standard for diagnosis of PVRL is detection of malignant lymphoid cells in the eye, including the retina, vitreous body, and optic nerve. Surgical procedures include diagnostic vitrectomy, puncture of anterior chamber, chorioretinal biopsy, and diagnostic enucleation [4, 8]. Currently, diagnostic vitrectomy is the most common method, and detection of lymphoma cells in vitreous sample is essential. Mudhar and Sheard revealed that specimens from pars plana

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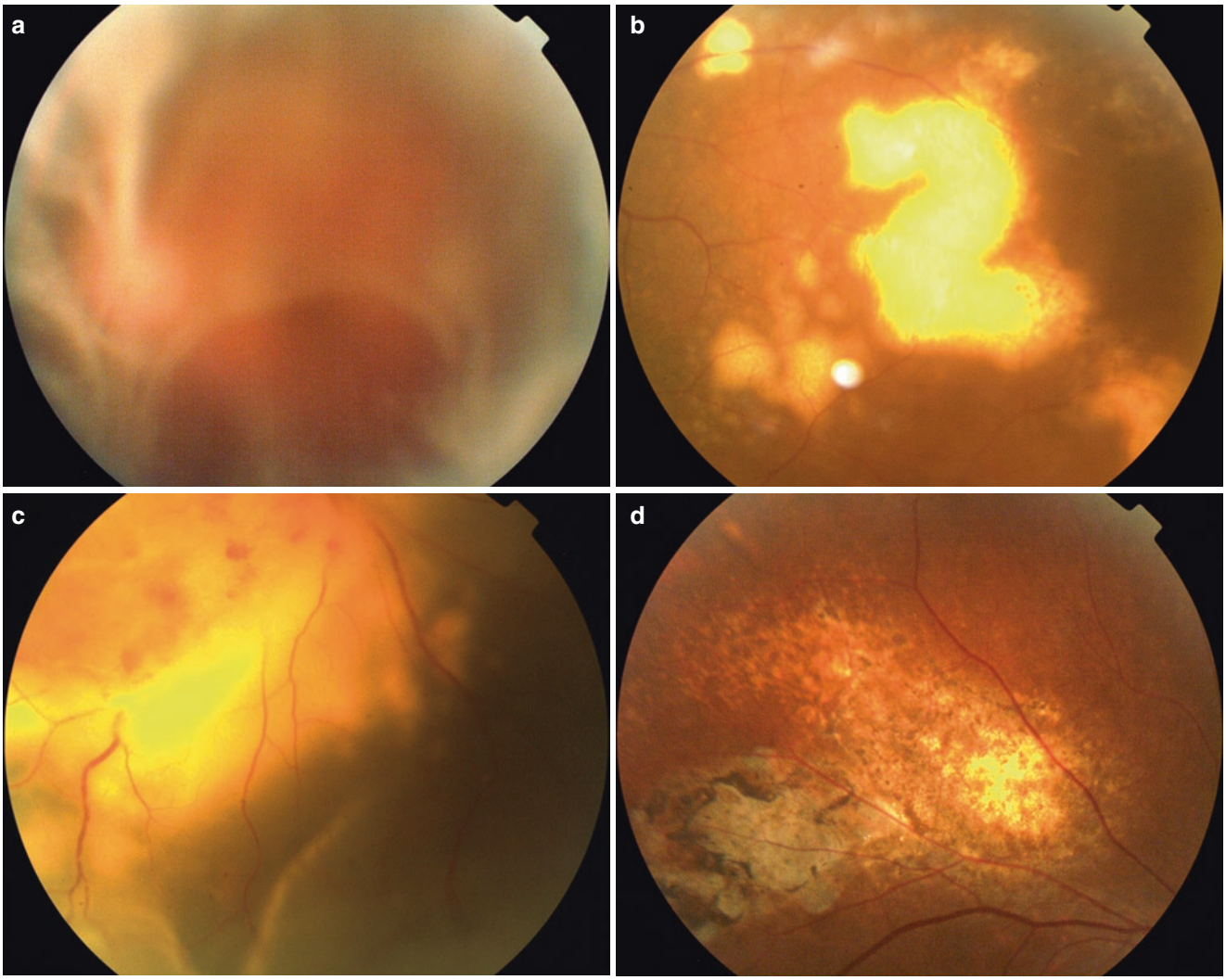

Fig. 19.1 Ocular features of PVRL. (**a**) Vitreous haze. (**b**) Multifocal creamy infiltrative lesions in the deep retina. (**c**) Exudative retinal detachment with subretinal lesions. (**d**) RPE atrophy after treatment

vitrectomy had an average cellularity of 31×, which is greater than specimens from core vitreous biopsy, so they speculated that the cells were more concentrated in the cortical vitreous body [9]. We generally use standard three-port pars plana vitrectomy to collect 1–2 mL undiluted vitreous biopsy without infusion for cytological examination. After that, open the infusion and collect some dilute vitreous sample for other examinations. Some authors suggested low cut rate and gentle aspiration during the vitrectomy [10, 11].

Because of the small amount of sample and cell fragility, diagnosis of PVRL is usually difficult to confirm [8]. It is reported that >40% of vitreous samples may remain without diagnosis after vitrectomy [12]. Promptly and properly handling the vitreous sample is very important, because the lymphoma cells are too fragile to survive. With the development of surgical techniques, cell preservation in culture medium, and cytological examination techniques, more PVRL cases were diagnosed in recent years. Ranty and colleagues showed a protocol of optimized management of vitreous samples in their study [13]. They suggested to preserve the vitreous sample in culture medium containing RPMI-1640, decomplemented fetal bovine serum, and gentamicin, and perform the whole procedure at 4 °C. Cytological examination with May–Grünwald–Giemsa staining and immunocytochemistry were performed on cytospins. With special focus on pre-analytical steps, diagnostic performance was improved [13].

The other reason for low diagnostic rate is corticosteroid treatment before diagnostic vitrectomy. Almost all of the experts agreed that negative results are common in the first diagnostic vitrectomy biopsy with patients receiving corticosteroids or any immunosuppressive treatment [14]. Repeated operations for cytological examinations are needed when PVRL is highly suspected [10, 14].

19.3.2 Cytology and Immunohistochemistry

According to WHO lymphoma classification, PVRL in most cases is subtyped as diffuse large B-cell lymphoma (DLBCL). Giemsa or Diff-Quick staining is better to detect the characteristics of malignant B cells [7]. Lymphoma cells are characterized by minimal basophilic cytoplasm and prominent nucleoli (Fig. 19.2) [15]. Necrosis and apoptosis, as well as reactive inflammatory cells, are frequently observed in these tumor cells, so the diagnosis is more difficult [7, 15].

Monoclonality immunophenotype supports the cytological diagnosis of lymphoma. Immunohistochemically, B cells from PVRL are characterized by CD79a+, CD19+, CD20+, PAX-5+, BCL2+, IRF4/MUM1+, etc., as well as monotypical for IgM [15]. Ki-67 staining is usually very high in PVRL patients, showing the rapid growth of tumor cells.

19.3.3 Flow Cytometry

Flow cytometry is a useful technique to obtain immunophenotyping, and works similar to immunocytological techniques. Flow cytometry allows the simultaneous application of multiple monoclonal antibodies to a small number of suspected lymphoma cells, thus allowing the use of larger detection panel [16]. But the problem of this method is contamination by heterogeneous population of B and T cells, and may cause difficulty to interpret the results [14]. Another problem with this method is background noise, which may mask signals from lymphoma cells when there are few interested cells, as is often the case in PVRL [5]. Meanwhile, flow cytometric immunophenotyping usually requires relatively larger amount of sample, but ocular specimens are often limited. In summary, the application of immunophenotyping analysis for PVRL detection using flow cytometry could be restricted.

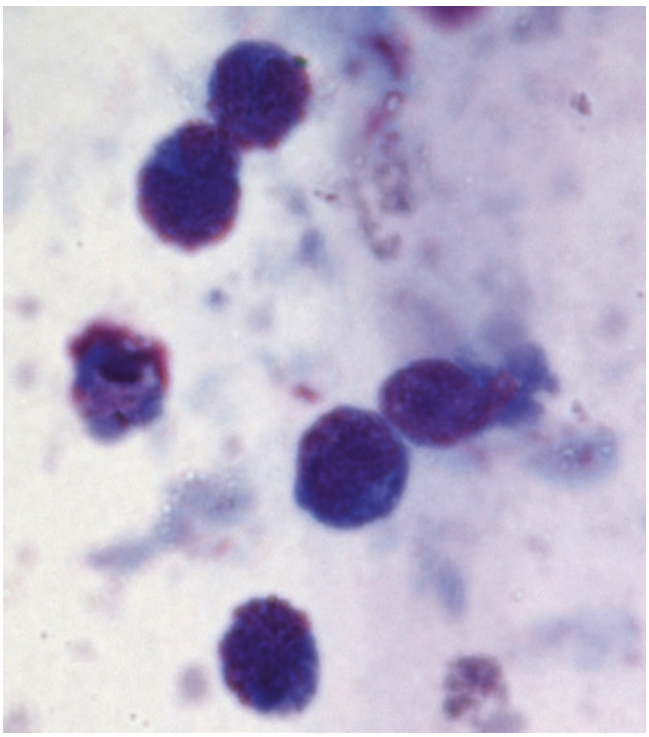

Fig. 19.2 Cytology of PVRL cells in the vitreous

19.3.4 Molecular Analyses

Microdissection and monoclonal rearrangement are used in the molecular analysis for PVRL. Relative pure atypical lymphoid cell population (PVRL cells) from cytological or histopathological slides is selected using microdissection, and DNA and RNA are extracted and analyzed to characterize the cells [14]. Monoclonal rearrangements such as immunoglobulin heavy chain (IgH) and T-cell receptor (TCR) genes can be detected. Chan reported a series of 57 PVRL patients; IgH rearrangements were demonstrated in all 50 tested cases [17]. Wang and colleagues have observed a series of 208 cases with masquerade syndrome; both the sensitivity and specificity of molecular markers in diagnosis of PVRL are higher than 95% [18]. Although gene rearrangement has high sensitivity, specificity, predictive value, and efficiency for the diagnosis of PVRL, IgH gene rearrangements are not indication of malignant lesions, and should be considered as adjuncts to improve diagnosis [5].

19.3.5 Intraocular Cytokine

High vitreous IL-10 level was first detected in three B-cell PVRL patients in 1995 [19]. Since then more ocular fluid samples of PVRL patients were tested to confirm the elevation of IL-10 [18, 20, 21]. In a series of 51 lymphoma patients and 108 uveitis patients, a cutoff of 50 pg/mL IL-10 in aqueous humor had a sensitivity and specificity of 0.89 and 0.93, respectively, for lymphoma. A cutoff value of 400 pg/mL IL-10 in the vitreous was associated with a specificity and sensitivity of 0.99 and 0.80, respectively [20]. The mean level of IL-6 and IL-10 in vitreous samples of uveitis patients was different from PVRL patients, but overlapping existed in some cases [18, 21]. Combination of the IL-10/IL-6 and IL-10/IFNγ ratios can be used to identify PVRL from uveitis samples [21]. Besides IL-10, levels of various immune mediators in the vitreous elevated, such as BCA-1, bFGF, Fas ligand, and RANTES, indicating the possibility that these factors are involved in the pathophysiology of vitreoretinal B-cell lymphoma [22].

Ecker and colleagues discovered that the concentration of different cytokines in the vitreous and aqueous humor was

different, but cytokine ratio was constant [23]. Fisson et al. also analyzed cytokines in the aqueous humor and vitreous, and reached the same conclusion [21]. The result is quite important because aqueous humor is much easier and safer to obtain, and multiple samples can be acquired. Measurement of IL-10 in the aqueous humor can be used as screening test to determine whether vitreous biopsy is indicated [24], as well as indicators for therapeutic effects and PVRL recurrence [25].

19.3.6 Updates on Probable Diagnostic and Estimated Methods

Tuo and Chan proposed that micro-ribonucleic acid (microRNA) in ocular fluid could be used as a novel marker for the diagnosis of PVRL. Quantification of ocular microRNA-155 might be helpful in the differential diagnosis of primary vitreoretinal B-cell lymphoma and uveitis [26]. However, for the diagnosis of PVRL, vitreous microRNA-155 level had no advantage over ratio of vitreous IL-10 and IL-6 levels.

The same MyD-88 L265P mutation has been shown to occur in about 15% of cases of systemic diffuse large B-cell lymphoma. Pulido and colleagues found that MYD-88 L265P constitutive activation mutations were present in some cases of diffuse large B-cell PVRL [27]. Bonzheim and colleagues identified MYD88 mutations in 20 of 29 confirmed PVRL cases. Detection of MYD88 mutations has improved the diagnosis rate of vitreoretinal B-cell lymphoma. Detection of MYD88L265P will enable more timely treatment and might be useful in monitoring treatment response, and may improve the prognosis of PVRL/PCNSL patients ultimately [28].

As mentioned before, high levels of IL-10 are related to rapid progression of vitreoretinal B-cell lymphoma, as well as PCNS of B-cell origin. Ramkumar and colleagues found IL-10 (-1082) G→A SNP with the GA genotype to be associated with PVRL and PCNSL [29]. It suggested that the IL-10 (-1082) A allele was a risk factor for higher IL-10 levels in PVRL and PCNSL [29].

19.4 Treatment

In 2011, the International Primary Central Nervous System Lymphoma Collaborative Group Symposium recommended the following guidelines of PVRL treatment [3]:

1. For patients without CNS or systemic involvement:
   If only one eye is involved, use local therapy with intravitreal methotrexate, intravitreal rituximab, or 30–35 Gy of external beam radiotherapy (EBRT).
   If both eyes are involved, there is still a preference toward local therapy, but systemic chemotherapy has been suggested in addition to intravitreal medications for bilateral cases.
2. For patients with CNS involvement:
   Systemic treatment is recommended, including chemotherapy in conjunction with local therapy, and whole-brain radiotherapy in conjunction with ocular radiotherapy.

19.4.1 Systemic Therapy

High-dose methotrexate is the most commonly used intravenous chemotherapy, and the doses should reach at least 3 g/m^2 in order to penetrate the blood–brain barrier and yield cytotoxic levels in the cerebrospinal fluid. In order to improve responses, other chemotherapeutic agents such as cytarabine are added [30]. High-dose methotrexate is reported to get a response rate of up to 72% when used alone and 94–100% in combination with other chemotherapeutic agents [5, 31].

Localized brain radiotherapy is usually used as first-line treatment of PCNSL [5]. Whole-brain radiotherapy (WBRT), high-dose methotrexate, and combined treatments make patients face greater risk of neurotoxicity. In patients with residual disease or disease progression, it is suggested to use localized brain radiotherapy with a total dose of 40–45 Gy with a 1.8–2.0 Gy dose per fraction [31].

In cases of refractory or relapsed PCNSL, high-dose chemotherapy combined with autologous stem-cell transplantation (HDC-ASCT) can be considered, and may be an efficient treatment [3].

19.4.2 Local Therapies

Local therapies include ocular radiotherapy and intravitreal chemotherapy. Up to now, there has been no randomized control study to compare the outcomes of these treatments, and no final conclusion that whether intravitreal chemotherapy or ocular radiation should be chosen as first-line therapy.

Intravitreal methotrexate was shown to be efficacious, and a dose of 0.4 mg methotrexate in 0.1 mL is recommended. The frequency of injections varied among different reports, ranging from twice a week to monthly during inductive therapy [32, 33]. The half-life of methotrexate in vitreous is approximately 5 days, so one injection probably has effect for approximately 3–4 weeks [34]. The primary goal of treating PVRL with intravitreal methotrexate is to reduce complications of intraocular lesions, as well as improve vision [8].

A common and characteristic side effect of intravitreal methotrexate is corneal epitheliopathy, which subsided when the injection interval increased [5, 32, 35]. It is reported that

paracentesis before the injection and oral folic acid supplements could minimize drug toxicity and reduce corneal epitheliopathy [35].

Ocular radiotherapy is used to control PVRL disease, maintain vision, and prevent CNS involvement. Radiotherapy alone could achieve high local control rates and improved visual acuity, but could not prevent lymphoma relapse [36, 37]. Complications of ocular radiotherapy include dry eye, cataract formation, radiation retinopathy, and local recurrence. With proper techniques, retinopathy and recurrence could be very low [8, 37].

19.4.3 Updates on PVRL Treatment

In order to reduce the number of methotrexate injections, a sustained-release device with methotrexate has been tested. It is a kind of biodegradable microneedle implant, releasing MTX for a period of more than 1 month, and no toxicity was detected in rabbit test [38].

Rituximab is a first-generation chimeric murine mAb against the CD20 antigen. There have been significant improvements in treatment outcomes for different kind of systemic non-Hodgkin's lymphomas after clinical use of rituximab [39]. Intravitreal rituximab at a dose of 1 mg appeared to be safe in rabbit eyes, and causes no side effects in eyes of five PVRL patients, resulting in reduction of tumor occurrence and growth [40, 41].

From limited reports of intravitreal rituximab for the treatment of PVRL in the literature, this method appears to be safe and effective in a majority of PVRL. Thus the number of intraocular MTX injections can be reduced to minimize the toxicity [39, 42].

Ublituximab is a promising glycoengineered anti-hCD20 mAb with a high affinity for FccRIIIa (CD16) receptors. Ben Abdelwahed and colleagues have found that single doses of intravitreal ublituximab had significant antitumor effect, and the effect was more obvious than the same dose of rituximab [43].

Th17 cell has been proved to participate in the onset of multiple autoimmune diseases. Galand and colleagues demonstrated that Th17-related cytokines may counteract tumor progression via IL-21 production, and Th17 cells as well as their related cytokines are hopefully to become an important adjuvant therapy for PVRL [44].

19.5 Conclusion

Primary vitreoretinal lymphoma is related to central nervous system disease and often masquerades as chronic posterior uveitis. Because it is frequently misdiagnosed at first presentation and the prognosis is poor, differential diagnosis is very important. Golden standard for the diagnosis of PVRL is detection of malignant lymphoid cells inside the eye. Diagnostic vitrectomy is the most common procedure to obtain ocular sample, and it is critical to process the vitreous specimen promptly and properly. A protocol for diagnosis of PVRL was built in our hospital in recent years. Seeing a patient older than 40, with bilateral uveitis of vitreous opacity or yellow subretinal lesions, we should appropriately suspect the diagnosis of PVRL. Enhanced MRI of the head is performed first. If the result of MRI is positive, lumbar puncture is done and cerebrospinal fluid is analyzed by hematologist and neurologists. Sometimes, we work with neurosurgeon to decide whether brain biopsy is needed. If the result of MRI is negative, paracentesis is performed and IL-10/IL-6 in the aqueous humor is measured to determine whether diagnostic vitrectomy is indicated. Cytology and immunohistochemistry examination of undiluted vitreous are done to confirm the diagnosis of PVRL. Gene rearrangement of diluted vitreous is an important auxiliary examination. Flow cytometry and intraocular cytokine detection are used when necessary.

Treatments of PVRL include systemic and local therapy. Systemic chemotherapy is recommended when CNS is involved. Intravitreal methotrexate and/or ocular radiotherapy are used for PVRL patients without brain involvement. Biodegradable microneedle implant loaded with methotrexate may reduce the number of methotrexate injections. Intravitreal anti-CD20 agent is a relatively new therapy, and seems safe and effective.

In summary, PVRL is a rare disease; as an ophthalmologist, we should appropriately consider the differential diagnosis of PVRL, obtain adequate sample for pathological evaluation, work closely with pathologists to clarify the diagnosis, and with hematologists and neurologists to treat and follow up the patients properly.

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