



## Research Article

# Primary Vitreoretinal Lymphoma: A Retrospective Study of 20 Eyes

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**Purpose.** This study aimed to describe and analyze the clinical features of 20 eyes of 15 primary vitreoretinal lymphoma (PVRL) patients. **Methods.** This was a retrospective case series and a review of the literature. Fifteen PVRL patients (20 affected eyes) referred between February 2011 and December 2019 were recruited, and their medical records were retrospectively reviewed. **Results.** Among these 15 PVRL patients, seven were men (46.67%), and five had bilateral PVRL (33.33%). The median onset age was  $66 \pm 9.26$  years and six (40%) patients had central nervous system (CNS) involvement, and two of them died of CNS-related complications. The ocular symptoms varied from decreased vision to binocular diplopia. The ocular manifestations were diverse and involved both the anterior and posterior segments, including the vitreous cells, subretinal white-yellow lesions, cotton-wool spots, and ophthalmoplegia. The rate of misdiagnosis and failure to diagnose was 100%, and 30% of them were misdiagnosed as uveitis. We found five cases revealing rare characteristics of this malignancy. Among them, there were two cases with mild hypertensive retinopathy exhibiting cotton-wool spots, one case mimicking age-related macular degeneration (AMD), one case with systemic lupus erythematosus (SLE), and one patient had extraocular muscle involvement. To the best of our knowledge, we reported PVRL exhibiting cotton-wool spots as the main manifestation and coexisting with extraocular myopathy for the first time. **Conclusions.** PVRL is a rare intraocular malignancy that commonly masquerades as uveitis. As the clinical signs and symptoms are atypical, ophthalmologists must carefully examine patients to avoid misdiagnosis or a failure to diagnose. Cotton-wool spots and extraocular myopathy might be the dominant initial symptoms in PVRL patients, and AMD should be considered a differential diagnosis of PVRL. SLE patients under immunosuppressive treatment could have spontaneous PVRL.

## 1. Introduction

Primary vitreoretinal lymphoma (PVRL) is a rare malignancy that occurs in the retina or vitreous of the eye, comprising less than 0.01% of all ocular diseases [1, 2]. PVRL most commonly represents non-Hodgkin's lymphoma (NHL), and 90% of cases have diffuse large B-cell lymphoma (DLBCL) [3]. The clinical features of PVRL are nonspecific, including the presence of large, nonclumped vitreous cells

and white-yellow subretinal deposits associated with solid retinal pigment epithelium (RPE) detachments [4], making it one of the most common masquerade syndromes [5, 6]. The differential diagnosis of PVRL is wide and includes infectious and noninfectious uveitis, retinal vasculitis, white dot syndrome, metastatic cancers, and so on [7–12]. The delay in diagnosis of PVRL varies from 4 to 40 months [8, 13, 14], and up to 90% of PVRL cases develop central nervous system (CNS) lymphomas during disease

progression, resulting in a poor prognosis and a low survival rate [1, 15]. Therefore, establishing an early diagnosis of PVRL allows for early treatment, which may be beneficial to reducing the mortality rate [16].

In the current study, we described and analyzed the clinical features of 15 PVRL patients to extend the existing knowledge of this ocular malignant tumor, hoping to facilitate an earlier diagnosis by ophthalmologists.

## 2. Methods

This is a retrospective case series. Written informed consent was acquired from all of the patients or their next of kin. The study adhered to the tenets of the Declaration of Helsinki and obtained Institutional Review Board approval from Zhongshan Ophthalmic Center, Sun Yat-sen University (IRB number: IIT2022057).

Patients with biopsy-proven PVRL from Zhongshan Ophthalmic Center, Sun Yat-sen University (ZOC), and the First Affiliated Hospital of Sun Yat-sen University (FAH-SYSU) between February 2011 and December 2019 were included. The diagnosis of PVRL was based on a positive ocular tissue biopsy by vitrectomy or vitreous aspirate. For cases in the absence of ocular tissue biopsy, the diagnosis depended on a positive extraocular tissue biopsy by bone marrow aspirate or lumbar puncture. The clinical specimens were sent to senior pathologists to assess the pathological features by morphological assessment, immunocytochemistry, or molecular techniques. Exclusion criteria included ocular and head trauma, ocular surgery history, extraocular lymphoma history, systemic infectious diseases, acquired immune deficiency syndrome, and other immunodeficiency diseases.

Medical records of the PVRL patients, including initial symptoms, medical history, best-corrected visual acuity (BCVA), IOP with a Goldmann applanation tonometer, slit-lamp biomicroscopy, ophthalmoscopy, fundus photography (CR-2 AF, Digital Retinal Camera, Canon, Japan), optical coherence tomography (OCT, Spectralis OCT, Heidelberg Engineering, Germany), and magnetic resonance imaging (MRI), were searched in the case management systems of ZOC and FAHSYSU or obtained from the patients themselves. Coexisting systemic syndromes were evaluated by experienced oncologists or neurologists at FAHSYSU at the time of diagnosis. Patients were followed by the ophthalmologist and their medical oncologist every six to 12 months, and the data regarding chemotherapy and radiotherapy were also collected. Cases with special characteristics are described in detail. A statistical description was generated using SPSS for Windows, version 26.0.

## 3. Results

Fifteen patients (20 affected eyes) with biopsy-proven PVRL were recruited for our study, including seven men (8 eyes) and eight women (12 eyes). Five patients (33.33%) had bilateral PVRL at presentation. The median age at diagnosis was  $66 \pm 9.26$  years (range, 49–81 years) with a median delay in diagnosis of  $5 \pm 4.35$  months (range, 0–14 months). The

median follow-up time was  $28.5 \pm 10.60$  months (range, 12–45 months). During follow-up, six patients (40%) subsequently developed CNS lymphoma, and two of them died of CNS-related complications. Neither acquired immunodeficiency syndrome nor other immunodeficiency diseases were found in these patients.

All 15 patients had varying degrees of ocular signs as their first symptoms, and the most common signs were decreased vision (9 patients, 11 eyes) and floaters (7 patients, 9 eyes). Other symptoms included photophobia in four patients (5 eyes), ocular pain in three patients (3 eyes), and binocular diplopia in one patient (1 eye). Six patients (40%) had constitutional symptoms such as fever, headache, hypomnesia, and aphasia (Table 1). On the ocular examination, the BCVA at the patients' first visit varied from light perception to 20/25. The median baseline IOP was  $14 \pm 7.69$  mmHg (range, 8–38 mmHg), and four eyes (20%) had elevated IOP.

Clinical signs in both the anterior and posterior segments of the eyes were observed in all PVRL patients (Table 2). The characteristics of the anterior segment included conjunctival and episcleral congestion (5 eyes), corneal edema (2 eyes), keratic precipitates (KP) (6 eyes), aqueous flare (7 eyes), iris posterior synechiae (2 eyes), rubeosis iridis (1 eye), sluggish light reflex (4 eyes), and asymmetric cataract (1 eye). The Tyndall signs of aqueous flare were mild to moderate with a few aqueous humor cells (Figures 1(a) and 1(b)).

The posterior segment abnormalities of the PVRL eyes had variant clinical features. All 20 affected eyes exhibited varying degrees of vitreous opacity (Figure 1(c)). Seventeen of them underwent retinal examinations, while three eyes with severe cataracts or vitreous opacities could not be examined. All these 17 eyes exhibited vitreous cells and RPE irregularities in the fundus. Punctate subretinal white-yellow lesions were found in 12 eyes, which showed different sizes with obscured boundaries and predominantly clustered in the posterior poles (Figure 2). Some white-yellow foci were easily missed by ophthalmoscopy observation (Figure 3(a)). Retinal hemorrhages were present in 5 eyes. Two eyes from two different patients exhibited cotton-wool spots (Figures 3(b) and 3(c)). Other manifestations included optic nerve edema (4 eyes) or atrophy (2 eyes), macular edema (3 eyes), hard exudates (3 eyes), sub-RPE infiltration lesions (3 eyes), retinal vascular leakages (2 eyes), retinal neovascularization (1 eye), and exudative retinal detachment (1 eye). Ophthalmoplegia, which is a periorbital sign, was also found in one patient in our study.

Before biopsy confirmation of PVRL, the patients were diagnosed with various masquerading conditions (Table 2). The most common misdiagnosis was uveitis in six eyes (30%). Other diagnoses included conjunctivitis, scleritis, vitritis, age-related macular degeneration (AMD), infectious endophthalmitis, retinal vasculitis, neovascular glaucoma, hypertensive retinopathy, Purtscher's retinopathy, and Tolosa-Hunt Syndrome. Three patients were referred for an unknown disease. Nearly half of the patients (7 cases) had neurological symptoms at approximately nine months (range, 7–18 months) after developing ocular conditions.

TABLE 1: Symptomatology of 15 PVRL patients with 20 affected eyes.

| Ocular symptoms*        | Patients (%) | Eyes (%) |
|-------------------------|--------------|----------|
| Decreased vision        | 9 (60)       | 11 (55)  |
| Floaters                | 7 (46.67)    | 9 (45)   |
| Photophobia             | 4 (26.67)    | 5 (25)   |
| Ocular pain             | 3 (20)       | 3 (15)   |
| Binocular diplopia      | 1 (6.67)     | 1 (5)    |
| Constitutional symptoms |              |          |
| Fever                   | 1 (6.67)     |          |
| Headache                | 2 (13.33)    |          |
| Hypomnesia              | 2 (13.33)    |          |
| Aphasia                 | 1 (6.67)     |          |

\*Eight patients (53.33%) had more than 2 symptoms. PVRL, primary vitreoretinal lymphoma. Eight patients (53.33%) had more than 2 symptoms. PVRL, primary vitreoretinal lymphoma.

TABLE 2: Clinical characteristics and prior diagnosis of 20 eyes with PVRL.

| Clinical characteristics (>1 possible) | Number (%)    |
|--|---------------|
| Anterior segment                       | <i>n</i> = 20 |
| Conjunctival and episcleral congestion | 5 (25)        |
| Corneal edema                          | 2 (10)        |
| Keratic precipitates (KP)              | 6 (30)        |
| Aqueous flare                          | 7 (35)        |
| Iris posterior synechiae               | 2 (10)        |
| Rubeosis iridis                        | 1 (5)         |
| Sluggish light reflex                  | 4 (20)        |
| Asymmetric cataract                    | 1 (5)         |
| Posterior segment*                     | <i>n</i> = 17 |
| Vitreous cells                         | 17 (100)      |
| RPE irregularities                     | 17 (100)      |
| Subretinal white-yellow lesions        | 12 (70.59)    |
| Retinal hemorrhages                    | 5 (29.41)     |
| Cotton-wool spots                      | 2 (11.76)     |
| Optic nerve edema                      | 4 (23.53)     |
| Optic nerve atrophy                    | 2 (11.76)     |
| Macular edema                          | 3 (17.65)     |
| Hard exudates                          | 3 (17.65)     |
| Sub-RPE infiltration                   | 3 (17.65)     |
| Retinal vascular leakages              | 2 (11.76)     |
| Retinal neovascularization             | 1 (5.89)      |
| Exudative retinal detachment           | 1 (5.89)      |
| Periorbital                            | <i>n</i> = 1  |
| Ophthalmoplegia                        | 1 (100)       |
| Prior diagnosis (>1 possible)          | <i>n</i> = 20 |
| Conjunctivitis                         | 2 (10)        |
| Scleritis                              | 1 (5)         |
| Uveitis                                | 6 (30)        |
| Vitritis                               | 2 (10)        |
| AMD                                    | 1 (5)         |
| Infectious endophthalmitis             | 1 (5)         |
| Retinal vasculitis                     | 1 (5)         |
| Neovascular glaucoma                   | 1 (5)         |
| Hypertensive retinopathy               | 2 (10)        |
| Purtscher's retinopathy                | 1 (5)         |
| Tolosa-Hunt syndrome                   | 1 (5)         |
| Uncertain                              | 3 (15)        |

\*Retinal examinations were performed in 17 eyes. PVRL, primary vitreoretinal lymphoma; AMD, age-related macular degeneration.

Cerebral lesion(s) were found in these patients and they were finally diagnosed with DLBCLs by pathological examination. Individuals in our study received an array of treatments before being diagnosed with PVRL, including steroids in eight patients, topical in eight, and oral in four. Other recorded therapies were topical antibiotics, topical glaucoma drops, nonsteroidal anti-inflammatory, vitrectomy, and intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF). Three patients received no treatment before diagnosis.

Five specific cases require further elaboration. Three patients suffered from systemic diseases, including systemic hypertension in two patients and systemic lupus erythematosus (SLE) in one patient. When they came to the ophthalmic clinic, their ocular abnormalities were first considered to be retinopathy associated with these chronic systemic diseases. For the two patients with hypertension, their fundus exhibited cotton-wool spots and micro-hemorrhagic foci that mimicked hypertensive retinopathy (Figure 3(a)) and Purtscher-like retinopathy (Figure 3(b)), respectively. However, as both patients had vitreous floaters indicating additional inflammatory signs, vitreous aspirates were performed at their follow-up visits and the diagnosis of DLBCL was established. For the patient with SLE, she had visual acuity deteriorating and her fundus examination showed retinal vasculitis and tiny subretinal white-yellow lesions. Punctate white-yellow loci were also found in these patients, but the lesions were tiny and easily missed under ophthalmoscopy examination. She was at an inactive stage of SLE and was currently under low-dose maintenance treatment with immunosuppressants and glucocorticoids. The final diagnosis of non-Hodgkin's lymphoma was established by vitreous biopsy. After local and systemic methotrexate chemotherapy, the number and size of cotton-wool spots and white-yellow lesions decreased. The fourth case was a 48-year-old male who had central vision loss for six months. His fundus examination revealed mild vitreous opacity and macular hard exudates with hemorrhagic lesions (Figure 3(c)). However, the hemorrhagic lesions were minimal under funduscopy and were neglected by the clinical doctor at the first visit. After exclusion of systemic and infectious diseases, he was diagnosed with dry AMD. The lesions had obviously expanded after a 3-month follow-up. Cytokine analysis of vitreous fluid found elevated IL-10 and IL-6 at 436.8 pg/ml and 93.6 pg/ml, respectively. A diagnostic vitrectomy was performed and the cytology and immunohistochemistry studies confirmed the diagnosis of DLBCL. Subsequent MRI of the brain and orbits found no intracranial or orbital space-occupying lesions. Another case was a 60-year-old woman. She complained of fever, binocular diplopia, and pain in the right eye and orbit for ten days after her first visit to the ophthalmic clinic. The BCVA was 20/40 in the right eye and 20/25 in the left eye. Ocular examination found mild lens opacity in both eyes and a few vitreous cells and exotropia position with limited movement toward the nasal direction in the right eye. An MRI showed a mildly enlarged right cavernous sinus. The primary diagnoses were established as cataract, vitritis, and Tolosa-Hunt syndrome. The patient was referred to the neurology clinic

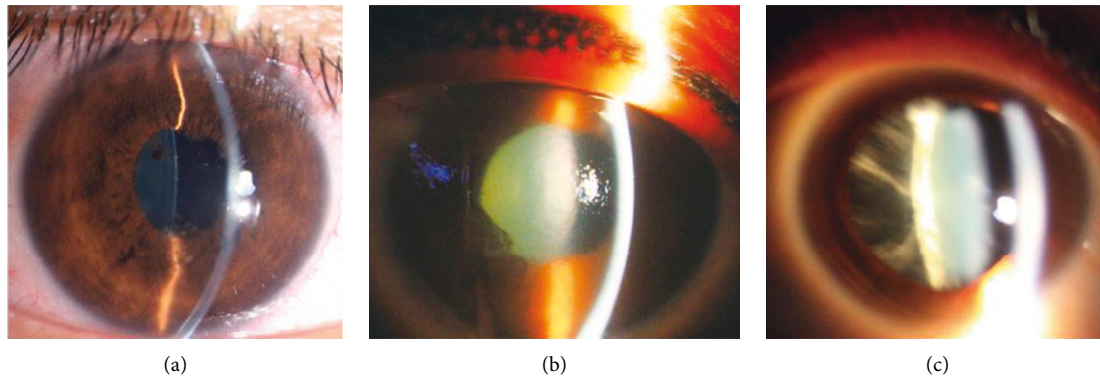


FIGURE 1: Anterior segment photography of primary vitreoretinal lymphoma (PVRL) patients. (a) The right eye of a 52-year-old female patient with PVRL shows moderate conjunctival and episcleral congestion, pigmented keratic precipitates, mild aqueous flare, and iris posterior synechiae, mimicking iridocyclitis. (b) The right eye of a 49-year-old female PVRL patient demonstrates severe corneal edema, mild aqueous flare, iris posterior synechiae, and cataract. She complained of mild eye irritation when she came to our clinic. (c) A 69-year-old male PVRL patient exhibits mild conjunctival and episcleral congestion, moderate cataract, and severe vitreous opacity with massive floaters in his right eye.

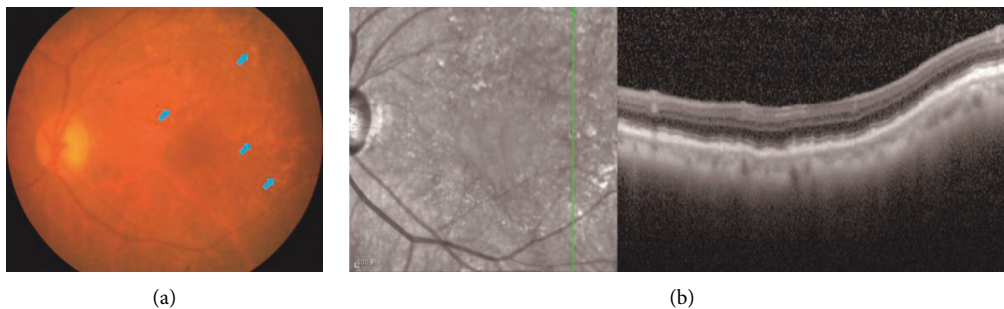


FIGURE 2: Fundus examination of the left eye of a 67-year-old male patient with primary vitreoretinal lymphoma. (a) Color fundus photography reveals RPE irregularities and subretinal white-yellow lesions with varied sizes and numbers in the posterior pole of the left eye (blue arrows). (b) The white-yellow lesions exhibit sub-RPE hyperreflective deposits on optical coherence tomography.

for further examination, and a cerebrospinal fluid test confirmed the diagnosis of NHL. After chemotherapy with rituximab and methotrexate, her symptoms gradually improved and the number of vitreous cells decreased. However, the patient died of neurological complications within two years.

#### 4. Discussion

In the current study, we investigated the clinical features of 20 eyes of 15 patients with PVRL to gain a better understanding of this disease, hoping to improve the early diagnosis rate and prolong survival as much as possible. We reported five cases revealing rare characteristics of this malignancy. Among them, two cases with mild hypertensive retinopathy exhibited cotton-wool spots, one case mimicked AMD, one case had SLE, and one patient had extraocular muscle involvement. To the best of our knowledge, we reported PVRL exhibiting cotton-wool spots as the main manifestation and coexisting with extraocular myopathy for the first time.

PVRL, a subset of primary central nervous system lymphoma (PCNSL), [9] is a rare intraocular lymphoid

malignancy, and its atypical clinical features make early diagnosis difficult [17]. As the symptoms of PVRL vary from decreased vision to binocular diplopia and ocular lesions involving both the anterior and posterior segments, the rate of misdiagnosis and failure to diagnose is high [12, 18, 19]. Mortality is up to 81% in PVRL patients with CNS involvement [20, 21]. Early systemic treatment for PVRL might delay the onset of CNS lymphomas and improve the prognosis [22].

In our study, 53.33% of the patients were men, and the median onset age was 66 years, and 40% of patients had CNS involvement, which is consistent with previous reports [8, 13]. However, only 33.33% of patients presented with binocular retinal lymphomas, and this lower proportion compared with previous studies [2, 23] might be related to the limited sample size and relatively short observation time. Although HIV and Epstein-Barr virus infection are important risk factors for PVRL, [9, 24, 25], none of our patients were infected.

The symptoms of 15 PVRL patients varied from decreased vision to binocular diplopia, and the ocular disorders involved both the anterior and posterior segments. The rate of misdiagnosis and failure to diagnose was 100% with

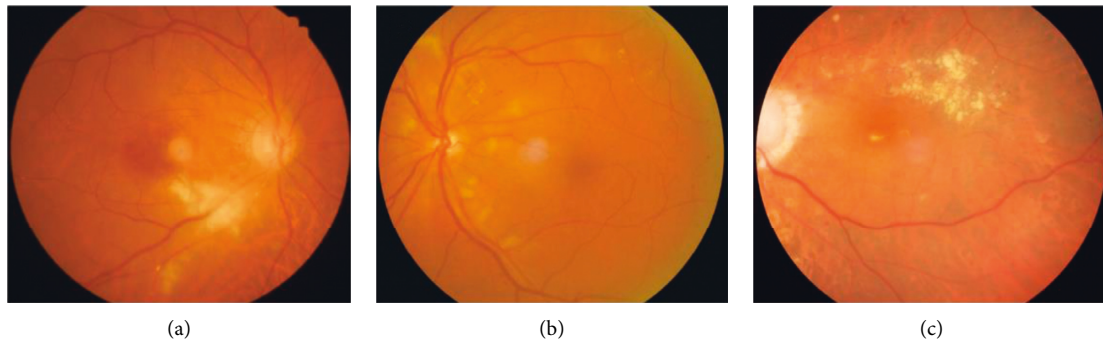


FIGURE 3: Color fundus photography of primary vitreoretinal lymphoma (PVRL) patients. (a) A 67-year-old male hypertension patient with PVRL presents with large integrated cotton-wool spots, with linear hemorrhagic lesions and punctate yellow-white spots in his right fundus. The retinal arteriolar is attenuated. The patient was misdiagnosed with hypertensive retinopathy. (b) A 52-year-old female PVRL patient shows Purtscher-like retinopathy. Color fundus photography of the left eye reveals multiple confluent cotton-wool spots around the optic nerve head and along the temporal arcades. Superficial dot hemorrhages, microaneurysms, and tiny yellow-white lesions are also visible in the posterior pole. (c) A 48-year-old PVRL male patient has multifocal yellow-white lesions and hemorrhagic loci in the macula of his left eye, resembling age-related macular degeneration.

an average delay in the final diagnosis of 5 months. Given the nonspecific symptoms and clinical signs that mimic ocular inflammatory conditions, most of the cases were misdiagnosed as uveitis (6/20 eyes, 30%), which is similar to previous studies [10, 18, 19]. As PVRL is the most common type of masquerade syndrome, it is challenging and vital to establish a correct diagnosis. Their nonspecific clinical features also share common features with other ocular diseases.

Cotton-wool spots were prominent fundus findings in two cases in our study. Hyun et al. reported a case with rapidly developing cotton-wool spots in both eyes as an initial sign of systemic NHL [26]. Retinal cotton-wool spots are considered a significant clue to systemic diseases, and they might be produced by a focal ischemic insult [27]. In PVRL pathogenesis, microinfarction by tumor emboli and immune-related vasculitis may contribute to this microvascular change. Nonetheless, cotton-wool spots are features of moderate hypertensive retinopathy [28]. For the differential diagnosis, hypertensive retinopathy should present the same or more severe degree of accompanying microangiopathy, such as arteriovenous nicking, hard exudates, and blot or flame hemorrhages, not consistent with our cases [29, 30]. Moreover, both cases had vitreous floaters indicating additional inflammatory signs. Then, vitreous aspirates were performed at their follow-up visits and the diagnosis of DLBCL was established.

Both PVRL and AMD exhibit invasion of the RPE and sub-RPE or subretinal deposits, making them have similar clinical manifestations [31]. The yellow-white sub-RPE or subretinal deposits at the macula in the early stage of PVRL resemble drusen in AMD. However, in PVRL cases, the lesion may become enlarged and confluent in a short period, and some patients have complaints of floaters because of vitreous cells. Sub-RPE vertical hyperreflective deposits on OCT may also be helpful in identifying diseases [3, 32]. Our patient previously diagnosed with Tolosa–Hunt syndrome is another misdiagnosed PVRL case. Tolosa–Hunt syndrome, characterized by recurrent painful ophthalmoplegia caused by granulomatous inflammation of the cavernous sinus

region, is a diagnosis of exclusion [33, 34]. The case in our study had clinical features similar to Tolosa–Hunt syndrome, including unilateral orbital pain, paresis of the third cranial nerve, and cavernous sinus, which resulted in an incorrect diagnosis. Ocular adnexal involvement might result from lymphoma infiltration into the superior orbital fissure and was coincident with the vitreoretinopathy, suggesting a special subtype of PCNSL. When middle-aged and elderly individuals suffer from painful ophthalmoplegia with simultaneous intraocular manifestations and constitutional symptoms, careful examinations and follow-ups are required to exclude other causes of disease.

For patients suffering from cardiovascular, endocrine, or autoimmune diseases, clinicians are inclined to establish an ocular diagnosis associated with these systemic disorders. There has been one case of PVRL with SLE reported in the previous literature [35]. SLE is a multisystemic autoimmune disease involving various organs and tissues. The incidence of retinopathy in SLE is between 3% and 29% and is related to disease activity [36]. Clinical findings of SLE retinopathy include cotton-wool spots, microaneurysms, dot hemorrhages, and hard exudate [37, 38]. Otherwise, SLE patients have a higher incidence of malignancy and are four times more likely to develop NHL than healthy people [39]. The possible explanations for the association between NHL and SLE include elevated cytokines, usage of immunosuppressive drugs, and functional defects of suppressor T-cells in SLE patients [35, 39]. The SLE case in our study had deteriorated visual acuity and retinopathy progression during an inactive stage of SLE, indicating that other pathogeneses, such as malignancy, may be involved.

The limitations of our study include its retrospective nature, the small number of patients given the rarity of this disease, and a lack of detailed clinical and pathological data for some patients.

## 5. Conclusions

Since PVRL is a rare and life-threatening disease, rapidly establishing the correct diagnosis is crucial to improving

patients' visual outcomes and survival. However, with its diversity and nonspecificity of clinical manifestations, a diagnosis can be challenging. Detailed and systemic examination as well as follow-up observation help in the early diagnosis of PVRL. The present study reveals that cotton-wool spots and extraocular myopathy might be the dominant initial symptoms in PVRL patients, and AMD should be considered a differential diagnosis of PVRL. SLE patients under immunosuppressive treatment could develop spontaneous PVRL.

### Data Availability

The detailed data used to support the findings of this study are available from the corresponding author upon request.

### Disclosure

Chong-De Long is lead contact.

### Conflicts of Interest

The authors report no conflicts of interest.

### Authors' Contributions

Jing-Yi Luo and Shi-Tong Yu equally contributed to this work.

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