CANCER DIAGNOSIS & PROGNOSIS
1: 69-75 (2021) doi: 10.21873/cdp.10010

Clinical Features of Primary Vitreoretinal Lymphoma: A Single-center Study

SATORU KASE[1], KENICHI NAMBA[1], DAIJU IWATA[1], KAZUOMI MIZUUCHI[1], TAKAKO ITO[1], KEITARO HASE[1], KAYO SUZUKI[1], MASAHIRO ONOZAWA[2], NOBUYOSHI KITAICHI[1,3] and SUSUMU ISHIDA[1]

[1]*Department of Ophthalmology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan;*
[2]*Department of Hematology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan;*
[3]*Department of Ophthalmology, Health Sciences University of Hokkaido, Sapporo, Japan*

Abstract. *Background/Aim: This study aimed to demonstrate the clinical outcomes of primary vitreoretinal lymphoma (PVRL). Patients and Methods: Seventeen patients with PVRL who had been treated at Hokkaido University Hospital were enrolled in this study. They were diagnosed based on their cytology, interleukin-10/-6 ratio, and immunoglobulin heavy chain (IgH) gene rearrangement. Results: Diagnostic tests detected cytological malignancy among 14 cases (82.3%), high interleukin-10/-6 ratios among 16 cases (94.1%), and IgH monoclonality in 13 cases (76.5%). Systemic corticosteroids were given to seven (41.2%) patients before their diagnosis of PVRL. Treatments after diagnosis comprised intravitreal methotrexate injection, local radiation, and intravenous chemotherapy for 11, seven, and five cases, respectively. Central nervous system and systemic involvements were observed in nine and one case, respectively, and these complications occurred at 3 to 43 months (mean=16 months) after initial ocular presentation. Conclusion: Many of our patients did not receive any systemic intervention, and almost half of patients with PVRL developed central nervous system involvement during their follow-up period.*

Correspondence to: Kenichi Namba, MD, Ph.D., Department of Ophthalmology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan. Tel: +81 117065944, Fax: +81 117065948, e-mail: knamba@med.hokudai.ac.jp

Key Words: Vitreoretinal lymphoma, diagnosis, treatment, central nervous system involvement.

Intraocular lymphoma is a vision-threatening malignant tumor that is likely life-threatening when it has invaded the central nervous system. Malignant lymphomas with intraocular involvement are pathologically classified as either vitreoretinal lymphoma (VRL) or uveal lymphoma. VRL comprises primary VRL (PVRL) and intraocular invasion of primary central nervous system lymphoma (PCNSL). The frequency of VRL has been shown to be low among patients who had recently consulted a uveitis clinic for a specific etiology (1). We recently reported that patients with VRL characteristically manifest vitreal haze, followed by subretinal infiltrates (2). For patients with these ocular findings, a differential diagnosis of VRL predominates, especially if these patients have medical histories of PCNSL or systemic lymphoma. The prognosis of secondary VRL is likely to depend on management of the primary extraocular lesions, and it appears poorer than the prognosis of PVRL (3).

On the contrary, early and accurate diagnoses of PVRL of patients without past medical histories are most challenging compared to those having such history because they have no specific clinical findings corresponding to PVRL. Moreover, according to a multicenter study (4), the rate of PVRL diagnosis *via* cytological analysis of vitreous specimens was not high, although cytology-based proof of malignant cells in the vitreous fluid is the most critical aspect of a definite diagnosis. We and other researchers have shown that a cell-block preparation using shed vitreous samples improved the rate of cytological PVRL diagnosis (5-7). However, about four-fifths of patients diagnosed with PVRL consequently developed CNS lesions during their lifetime (8). Therefore, importantly, ophthalmologists and uveitis specialists must share their knowledge of the clinical features of PVRL. Accordingly, the present study aimed to report treatment options and clinical outcomes for patients with PVRL at our single center.

Patients and Methods

This study was retrospective and observational. The Institutional Review Board of Hokkaido University approved this study with the use of clinical data (IRB number: 18-90). Informed consent was obtained by the opt-out method on a website explaining the procedures performed and the review of medical records; however, written informed consent was obtained from the representative patient for the case report and accompanying images.

Seventeen patients were diagnosed with PVRL at Hokkaido University Hospital from 2005 to 2016. Clinical features – including fundus examination findings, optical coherence tomography findings, diagnostic rates, ocular/systemic treatments, CNS involvement, and clinical outcomes – were searched for in patients' medical records. All patients had undergone diagnostic vitrectomy with a 23- or 25-gauge vitreous cutter (2, 9). Both undiluted vitreous fluids and diluted shed vitreous fluids were eventually isolated.

Patients were diagnosed with PVRL based on cytological malignancy, an interleukin (IL) 10/IL6 concentration ratio greater than 1, and monoclonal immunoglobulin heavy chain (*IgH*) gene rearrangement in surgically excised vitreous samples, according to our previous studies (2, 5). This study's exclusion criteria comprised a diagnosis of uveitis, a history of extraocular lymphoma, and the detection of extraocular lymphoma *via* a systemic survey during the patient's initial ocular presentation. Any presence of CNS involvement was carefully checked for using brain magnetic resonance imaging (MRI) and positron-emission tomography-computed tomography.

All patients diagnosed with PVRL were referred to our center's hematologist and neurologists, and their courses of treatment were determined. Most patients underwent only local treatments because of minor side-effects, and some patients required systemic therapy that was, in some cases, combined with local radiotherapy.

Systemic therapies comprised systemic chemotherapy, including intravenous rituximab/methotrexate/procarbazine/vincristine (R-MPV) chemotherapy and high-dose methotrexate injection. Whole-brain radiation therapy was included when patients were young (less than 50 years old) and for selected patients, in conjunction with hematologists and neurologists. Systemic chemotherapy was performed in combination with radiotherapy based on a previous protocol (10).

Local therapies in the current study comprised local external-beam radiation to the affected eye and repeated intravitreal methotrexate injection (IV-MTX). Local radiation was mostly performed up to 2012, and IV-MTX was performed thereafter. IV-MTX was performed once weekly for at least 8 weeks, until vitreous haze and subretinal infiltrates had diminished, at a dose of 400 μg in 0.1 ml in the *pars plana* using a 30-gauge needle. Patients further underwent IV-MTX maintenance therapy monthly for a year. The outcome of IV-MTX therapy was evaluated, and this evaluation was modified based on a previous report describing intravitreal rituximab administration (11). When the patient's vitreous haze had diminished and their subretinal infiltrates had become retinal atrophy, they were evaluated as having undergone complete remission.

Comparisons of cases at PVRL diagnosis and during CNS involvement between the study's clinically symptomatic and asymptomatic groups described below were performed with an unpaired Student's *t*-test. A *p*-value of less than 0.05 was considered statistically significant.

Results

Clinical features and diagnosis. Table I summarizes the clinical features of the patients with PVRL examined in this study. These patients comprised eight men and nine women. Their mean age at PVRL onset was 67 (range=47-87) years. Their mean follow-up duration was 55 (range=6-161) months. Bilateral and unilateral onset were seen for eight and nine patients, respectively, at their initial presentation. Various vitreous haze types were detected across patients, and 10 out of 17 cases involved aurora-type haze (12). Subretinal exudates emerged among six patients, which were also confirmed using optical coherence tomography. Fourteen (82.3%) patients were found to be cytologically positive for malignant cells through conventional smear cytology and cell-block preparations in four (23.5%) and 13 (76.5%) cases, respectively. Furthermore, the cell-block method demonstrated diffuse large B-cell lymphoma in all cases examined with additional immunocytochemistry. IL10/IL6 ratios greater than 1 were noted for 16 (94.1%) patients, with values of 3,141 (range=10-21,100) pg/ml for IL10 and 86 (range=9-567) pg/ml for IL6. *IgH* monoclonality was detected in 13 (76.5%) cases.

Treatments and clinical outcomes. Systemic corticosteroids were given to 7 (41.2%) patients before their PVRL diagnoses were made. Treatments after diagnosis comprised IV-MTX injection in 11 cases, local ocular radiation in seven cases, whole-brain radiation combined with high-dose IV-MTX in one case, and whole-brain radiation with R-MPV chemotherapy in three cases. Hematologists recommended against systemic chemotherapy for six patients due to old age and systemic complications, such as liver dysfunction and ischemic heart disease. Despite treatment, extraocular involvement with CNSL developed in nine cases, and systemic lymph node dissemination developed in one case. The time to extraocular onset of these conditions after PVRL diagnosis ranged from 3 to 43 months (mean=16.2 months). Three out of nine patients who developed CNS involvement were asymptomatic; the remaining six were symptomatic, with dementia in two cases and with facial deformity associated with one case each of facial nerve palsy, dysarthria, falls, and paralysis. The mean time between initial PVRL diagnosis and the onset of CNSL was 6.3±2.5 and 21.1±17.3 months in asymptomatic (N=3) and symptomatic (N=6) cases, respectively; however, no statistically significant difference was observed between the two groups. In this study, two patients eventually died of CNS relapse, at 78 and 124 months after their initial PVRL diagnoses (Table I).

Report of a representative case. A 48-year-old female (case 10) visited our hospital with a complaint of blurred vision in both eyes in December 2012. Her visual acuities were 1.2 in

Table I. *Clinical features of patients with primary vitreoretinal lymphoma (PVRL).*

Case	Age, years	Eye	Gender	Prior treatments	IL10, pg/ml	IL6, pg/ml	IgH	Cytology	TSI, months	Dissemination	Symptoms of systemic involvement	Treatment for PVRL	Follow-up, months	Status at study end
1	83	L	M	SC	1,300	51.6	–	+	6	CNS	Facial deformity	RT	40	Alive
2	65	B	F	SC	50	19.8	+	+	6	CNS	Asymptomatic	Radiation+ IV-MTX	78	Dead
3	72	R	F	SC	5,430	155	+	+	17	Systemic	Lymph node swelling	RT	76	Alive
4	56	B	M	SC	1,930	21.6	+	–	4	CNS	Asymptomatic	HD-MTX→ R-MPV	124	Dead
5	51	R	M	None	14,900	65	+	+	3	CNS	Dysarthria	HD-MTX+ WB-RT	116	Alive
6	80	L	F	SC	308	108	+	–	-	-	-	RT	11	Alive
7	69	L	F	None	21,100	56.5	–	+	9	CNS	Dementia	RT	63	Alive
8	82	R	M	LC injection	10	121	+	–	-	-	-	IV-MTX	161	Alive
9	75	B	M	LC injection	60	9.3	+	+	-	-	-	IV-MTX	8	Alive
10	48	B	F	SC	128	25.2	+	+	43	CNS	Dementia	WB-RT+ R-MVP→IV-MTX, AraC	43	Alive
11	59	L	F	LC injection	2,000	41.9	–	+	-	-	-	IV-MTX	11	Alive
12	72	B	F	LC injection	600	147	+	+	37	CNS	Paralysis	IV-MTX	37	Alive
13	85	B	M	None	166	17.6	+	+	-	-	-	RT+IV-MTX	32	Alive
14	87	B	F	None	1,140	567	+	+	-	-	-	RT+IV-MTX	6	Alive
15	58	B	M	SC	81	9.2	+	+	29	CNS	Falling	IV-MTX	29	Alive
16	47	L	M	None	775	10.4	+	+	9	CNS	Asymptomatic	WB-RT+ R-MPV+AraC+ IV-MTX	48	Alive
17	49	L	F	None	3,430	51	–	+	-	-	-	WB-RT+R-MPV+IV-MTX	46	Alive

AraC: Cytarabine; B: bilateral; CNS: central nervous system. F: female; HD-MTX: intravenous high-dose methotrexate; IgH: immunoglobulin heavy-chain gene rearrangements; IL: interleukin; IV-MTX: intravitreal methotrexate injection; L: left; LC: local corticosteroid; M: male; R: right; R-MPV: rituximab/methotrexate/procarbazine/vincristine; RT: radiotherapy; SC: systemic corticosteroids; TSI: time to systemic involvement; WB-RT: whole-brain radiotherapy.

her right eye (OD) and 0.7 in her left eye (OS). She had anterior chamber inflammation (2+ cells with keratic precipitates) and vitreous haze. Routine blood tests and chest X-rays at our uveitis clinic showed no abnormal findings. Oral prednisolone was given at 30 mg/day, and her visual acuity gradually improved. Prednisolone treatment was tapered and stopped in September 2013. However, this patient was referred to our hospital because vitreous opacity recurred with phlebitis-like findings in December 2013. Her past medical and family history were unremarkable. At the time of the patient's referral to our hospital, her visual acuities were 0.06 (1.2×−5.25D) OD and 0.06 (1.5×−5.00D) OS, with normal intraocular pressure. A slit-lamp examination revealed that the OD anterior chamber was clear, with a trace flare and occasional cells of the OS. A fundus examination revealed OD subretinal exudates and 1+ vitreous haze of the OS (Figure 1A and B). Pathological survey of the patient's vitreous fluid obtained during vitrectomy showed cytological malignancy for VRL, monoclonal *IgH* gene rearrangement, and high IL10/IL6 ratio (IL10: 128 pg/dl, IL6: 25.2 pg/dl). Gadolinium-enhanced MRI detected no brain abnormalities (Figure 2A). The patient was diagnosed with PVRL. She underwent IV-MTX (400 μg) eight times for both eyes. She also received whole-brain radiotherapy targeting the eye globes at a dosage of 23.4 Gy in addition to five courses of R-MPV chemotherapy. Her ocular lesions gradually regressed and then completely disappeared (Figures 1C and D). Although she had undergone routine MRI every 6 months, the patient suddenly complained of dysarthria 43 months after her initial ocular presentation. An MRI revealed massive white-matter lesions, indicating CNSL (Figure 2B). The patient then received high-dose MTX and cytarabine.

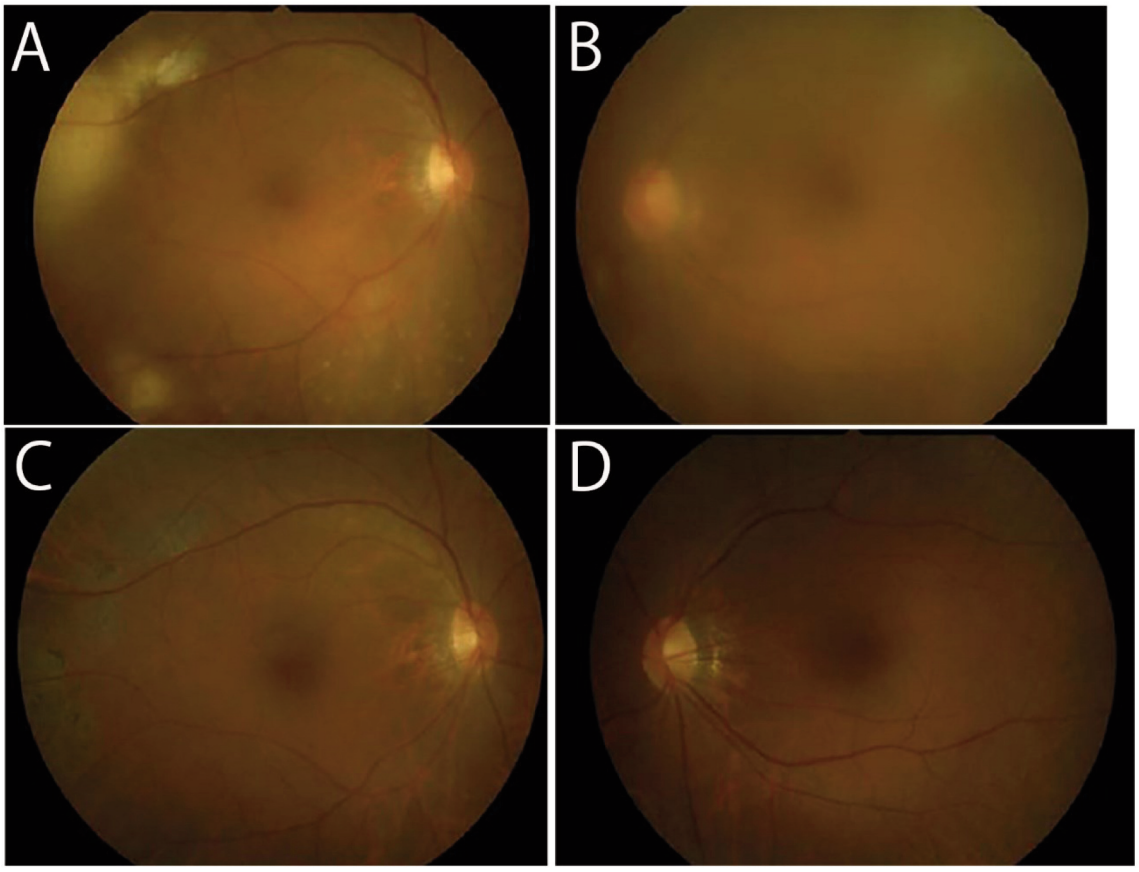

Figure 1. *A representative case with primary vitreoretinal lymphoma. Fundal examination revealed OD subretinal infiltrates (A) and OS diffuse vitreous haze (B). After treatment, the subretinal infiltrates became atrophic lesions (C), and the vitreous haze resolved (D).*

Discussion

In this study, systemic corticosteroids were administered to seven patients before they were definitively diagnosed with PVRL, indicating that idiopathic uveitis was considered as a possibility for some patients. PVRL has been regarded as a masquerading syndrome by ophthalmologists, since accurate diagnosis remains challenging when based on routine clinical examinations. Therefore, suspicious cases in which physicians can barely differentiate between PVRL and uveitis require early vitrectomy for diagnostic sampling, especially when ocular symptoms do not favorably respond to corticosteroid treatments.

Malignant cells were cytologically detected in the vitreous fluids of 14 PVRL cases in this study, together with IL10/IL6 ratios greater than 1 and monoclonal *IgH* gene rearrangement in 16 and 13 cases, respectively. Previous studies have demonstrated that a positive cytokine profile facilitates an accurate diagnosis of PVRL, with sensitivity and specificity both over 0.8, while the sensitivity and specificity of *IgH* monoclonality are 0.96 and 1.0, respectively (13, 14). In contrast, the positive rate of cytological diagnosis was not favorable, accounting for only about 20-40% among patients with VRL when conventional smear cytology was applied to the undiluted vitreous fluid (5, 14). In this study, cytological examinations were conducted with not only conventional smear cytology but also a cell-block preparation, which likely contributed to the study's relatively high diagnostic rate of VRL compared to others testing only conventional smear cytology (5).

In the present study, nine (52.9%) patients developed CNS involvement, for which the mean time that had elapsed from their initial PVRL diagnosis was 16.2 months. Of patients with PVRL, 65-90% were demonstrated to experience CNSL complications within 2 years of their PVRL diagnosis (8, 15), revealing higher rates of CNS involvement compared to our study. One reason for this difference may be this study's relatively short follow-up periods (less than 2 years in four cases). Another possible reason might be our university hospital's high cytological diagnostic rate (82.3%) using the

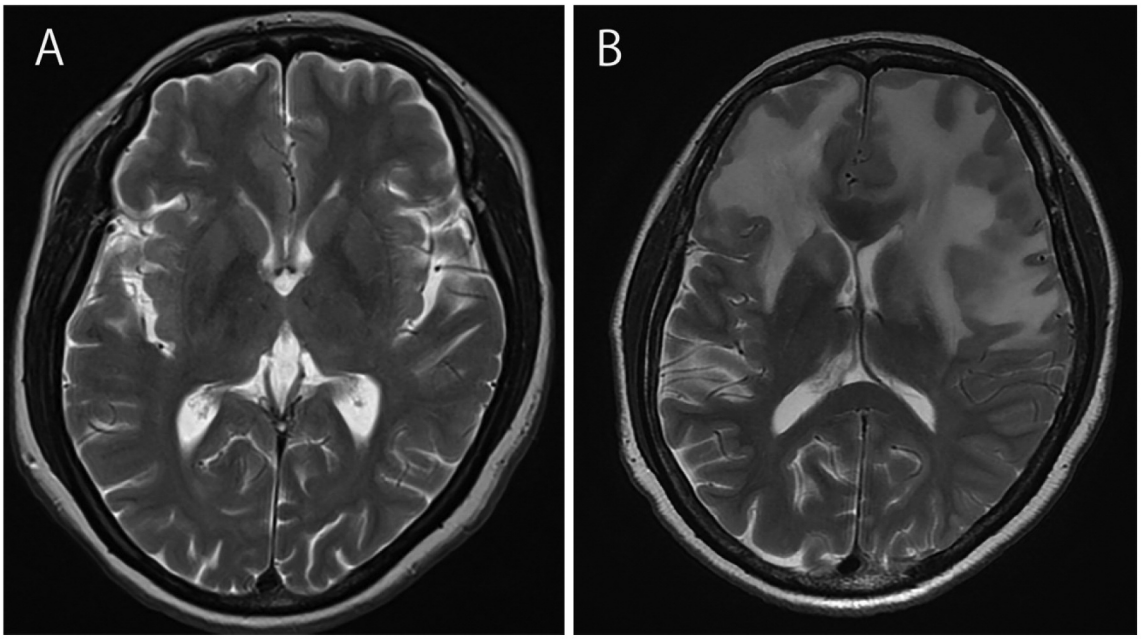

Figure 2. *A representative case with primary vitreoretinal lymphoma. A: Magnetic resonance imaging detected no tumor lesions upon initial presentation. B: Marked white-matter progression was detected several years after treatment.*

cell-block method. Cytological diagnosis is considered the gold standard for definitive VRL diagnosis by ophthalmologists, allowing for early diagnosis and immediate intervention with appropriate treatments. Further studies are needed to clarify the correlation between early PVRL diagnosis and the prevention of future CNSL.

The mean time that elapsed between PVRL diagnosis and CNS involvement in this study (16.2 months) was similar to previous reports (8, 15). It was possible to classify our patients with PVRL who suffered a later development of CNS involvement into asymptomatic and symptomatic cases. In asymptomatic cases, CNS involvement was routinely and repeatedly examined with brain MRI and coincidently detected before neurological symptoms appeared. In contrast, symptomatic patients had already presented with various neurological symptoms when CNS involvement was detected. Although no significant difference between these two groups was observed in the time taken to detect CNS involvement, detection in asymptomatic cases tended to be earlier than in symptomatic cases (6.3±2.5 *versus* 21.1±17.3 months). Routine and repeated brain imaging tests may contribute to the early detection of CNSL in patients with PVRL with no neurological symptoms.

After discussion with hematologists and neurologists, three patients (cases 10, 16, and 17 in Table I) were treated with a combination of whole-brain irradiation and systemic chemotherapy as their initial therapy, based on a previous protocol (10), when no CNS involvement was noted. Notably, these patients remain alive, and one of them is CNSL-free while the other two developed CNSL after 9 and 43 months of follow-up, respectively. Some reports have demonstrated the role of systemic chemotherapy or whole-brain radiotherapy in prolonging life prognoses among patients with PVRL. Cheah *et al*. retrospectively analyzed 11 patients with PVRL who had undergone R-MPV chemotherapy and local ocular radiation, combined with high-dose cytarabine. Their estimated 4-year overall survival rate was 76%, and three (36%) patients developed CNS involvement during the study's mean follow-up period of 4.2 years (16). Kaburaki *et al*. conducted a prospective study using R-MPV and low-dose whole-brain radiotherapy for 11 patients with PVRL. They concluded that their patients' 4-year overall survival rate was 89%, with CNS involvement occurring for one (9%) patient during the study's mean follow-up period of 4.1 years. Although white-matter abnormalities detected by brain MRI increased after the study's combined treatment regimen, only one patient developed mild cognitive impairment (17). Akiyama *et al*. analyzed a single-arm prospective study using systemic high-dose methotrexate, followed by IV-MTX, for 10 patients with PVRL. Four (40%) of their patients developed CNS involvement during the study's mean follow-up period of 2.5 years. Seven out of nine (78%) patients treated with IV-MTX alone (one patient was not followed-up) were shown to have survived after their initial PVRL diagnoses (18). These results reflect a fraction of real-world outcomes for patients with PVRL, suggesting that the majority

of patients can continue living for several years and avoid severe adverse events caused by systemic chemotherapy and radiation treatment. A multi-center study's 5-year survival rate was 61% for 217 patients with VRL examined, of whom 83% had PVRL (4). Klimova *et al*. recently reported that 5-year overall survival rate of patients with PVRL exceeded the corresponding rate for those with PCNSL with and without ocular involvement, highlighting the importance of combination therapy instead of local treatment alone (19). Since whether systemic chemotherapy or radiation treatment should be used for patients with PVRL remains controversial (20), comparative trials are needed alongside real-world outcomes to further improve prognosis of patients with PVRL.

In this study, we have summarized the concept of performing local and systemic PVRL treatments at our center. As a recent expert meeting confirmed the usefulness of IV-MTX in managing patients with VRL (21), we have also recognized IV-MTX as a useful local therapy to temporarily eliminate lymphoma cells in the eye. Both systemic chemotherapy and whole-brain irradiation are responsible for suppressing CNS involvement, but they are performed for younger patients without serious systemic complications and do have severe side-effects, including leukoencephalopathy, which threaten quality of life. Therefore, treatment strategies at our center are as follows: a) IV-MTX is tolerated and used only to preserve visual function, and b) systemic chemotherapy and whole-brain irradiation are performed to prevent CNS involvement, but this indication is limited.

Myeloid differentiation primary response 88 (*MYD88)* is known to activate nuclear factor-kappa B pathways, the specific mutation of which plays important roles in development of VRL. We recently published data showing no mutation of *MYD88* was detected among four patients with VRL, indicating that *MYD88* mutation might not frequently occur in patients in Hokkaido, Japan (2). On the other hand, these results differ from other research showing highly frequent *MYD88* mutation among patients with VRL (22). Miserocchi *et al*. recently demonstrated that *MYD88* mutation analyses are possible using the aqueous humor, and this finding contributed to differential diagnoses and patient management (23). Therefore, *MYD88* is likely a novel diagnostic and therapeutic target applicable worldwide (21), whereas the clinicopathological features of VRL might differ across races or origins. In Japanese populations, 5-year-survival rates have stood at about 60% for patients with VRL (4). Recently, Klimova *et al*. demonstrated that 5-year survival rates were high for patients with PVRL compared to those with ocular involvement of CNSL or PCNSL without ocular involvement (19). Since controversies persist regarding the use of systemic chemotherapy for patients with PVRL, further comparative studies between prospective clinical trials and real-world outcomes for patients with PVRL are needed.

The current study had some limitations. Firstly, it retrospectively included a small number of patients with PVRL and a relatively short follow-up period (mean=55 months). Secondly, no standardized follow-up method was available in terms of periodical brain MRI evaluation, although this study indicated a trend of shorter duration before CNS involvement in asymptomatic patients compared to symptomatic ones. The present study confirmed that, despite prompt intervention following an early definite diagnosis by our cytological methods, almost half of the patients with PVRL developed extraocular progression during follow-up, especially in the CNS.

Conflicts of Interest

The Authors declare that we have no conflicts of interest.

Authors' Contributions

SK collected all clinical data and wrote the article. KN, KS, KH, TI, and NK evaluated ophthalmological data and reviewed the article. MO analyzed neurological findings and reviewed the article. SI supervised the data collection and critically revised the article.

References

1 Ohguro N, Sonoda KH, Takeuchi M, Matsumura M and Mochizuki M: The 2009 prospective multi-center epidemiologic survey of uveitis in Japan. Jpn J Ophthalmol *56(5)*: 432-435, 2012. PMID: 22752308. DOI: 10.1007/s10384-012-0158-z

2 Kase S, Namba K, Kanno-Okada H, Onozawa M, Hidaka D, Iwata D, Mizuuchi K, Fukuhara T, Fukuhara J, Kitaichi N, Matsuno Y and Ishida S: Immunohistochemical and immunocytochemical analyses in patients with vitreoretinal lymphoma. Ocul Immunol Inflamm *28(1)*: 147-155, 2020. PMID: 30335535. DOI: 10.1080/09273948.2018.1533984

3 Karakawa A, Taoka K, Kaburaki T, Tanaka R, Shinozaki-Ushiku A, Hayashi H, Miyagi-Maeshima A, Nishimura Y, Uekusa T, Kojima Y, Fukayama M, Kurokawa M and Aihara M: Clinical features and outcomes of secondary intraocular lymphoma. Br J Haematol *183(4)*: 668-671, 2018. PMID: 29143310. DOI: 10.1111/bjh.15005

4 Kimura K, Usui Y, Goto H and Japanese Intraocular Lymphoma Study Group: Clinical features and diagnostic significance of the intraocular fluid of 217 patients with intraocular lymphoma. Jpn J Ophthalmol *56(4)*: 383-389, 2012. PMID: 22661396. DOI: 10.1007/s10384-012-0150-7

5 Kase S, Namba K, Iwata D, Mizuuchi K, Kitaichi N, Tagawa Y, Okada-Kanno H, Matsuno Y and Ishida S: Diagnostic efficacy of cell block method for vitreoretinal lymphoma. Diagn Pathol *11*: 29, 2016. PMID: 26987877. DOI: 10.1186/s13000-016-0479-1

6 Kanno-Okada H, Takakuwa E, Tagawa Y, Kase S, Hatanaka KC, Hatanaka Y, Namba K, Mitsuhashi T and Matsuno Y: Cytopathologic findings of cell block materials from the vitreous: Diagnostic distinction between intraocular lymphoma and non-lymphomatous diseases. Pathol Int *67(7)*: 342-349, 2017. PMID: 28590047. DOI: 10.1111/pin.12551

7 Raparia K, Chang CC and Chévez-Barrios P: Intraocular lymphoma: Diagnostic approach and immunophenotypic findings in vitrectomy specimens. Arch Pathol Lab Med *133(8)*: 1233-1237, 2009. PMID: 19653716. DOI: 10.1043/1543-2165-133.8.1233
8 Chan CC, Rubenstein JL, Coupland SE, Davis JL, Harbour JW, Johnston PB, Cassoux N, Touitou V, Smith JR, Batchelor TT and Pulido JS: Primary vitreoretinal lymphoma: A report from an international primary central nervous system lymphoma collaborative group symposium. Oncologist *16(11)*: 1589-1599, 2011. PMID: 22045784. DOI: 10.1634/theoncologist.2011-0210
9 Pulido JS, Johnston PB, Nowakowski GS, Castellino A and Raja H: The diagnosis and treatment of primary vitreoretinal lymphoma: A review. Int J Retina Vitreous *4*: 18, 2018. PMID: 29760948. DOI: 10.1186/s40942-018-0120-4
10 Morris PG, Correa DD, Yahalom J, Raizer JJ, Schiff D, Grant B, Grimm S, Lai RK, Reiner AS, Panageas K, Karimi S, Curry R, Shah G, Abrey LE, DeAngelis LM and Omuro A: Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: Final results and long-term outcome. J Clin Oncol *31(31)*: 3971-3979, 2013. PMID: 24101038. DOI: 10.1200/JCO.2013.50.4910
11 Cicinelli MV, Marchese A, Miserocchi E, Giuffré C, Berchicci L, Querques G, Bandello F and Modorati GM: Retinal and choroidal changes of vitreoretinal lymphoma from active to remission phase after intravitreal rituximab. Ocul Immunol Inflamm *28(4)*: 637-646, 2020. PMID: 31393199. DOI: 10.1080/09273948.2019.1616769
12 Marchese A, Miserocchi E, Giuffrè C, Cicinelli MV, Querques G, Bandello F and Modorati G: Aurora borealis and string of pearls in vitreoretinal lymphoma: Patterns of vitreous haze. Br J Ophthalmol *103(11)*: 1656-1659, 2019. PMID: 30709808. DOI: 10.1136/bjophthalmol-2018-313491
13 Cassoux N, Giron A, Bodaghi B, Tran TH, Baudet S, Davy F, Chan CC, Lehoang P and Merle-Béral H: IL-10 measurement in aqueous humor for screening patients with suspicion of primary intraocular lymphoma. Invest Ophthalmol Vis Sci *48(7)*: 3253-3259, 2007. PMID: 17591896. DOI: 10.1167/iovs.06-0031
14 Sugita S, Takase H, Sugamoto Y, Arai A, Miura O and Mochizuki M: Diagnosis of intraocular lymphoma by polymerase chain reaction analysis and cytokine profiling of the vitreous fluid. Jpn J Ophthalmol *53(3)*: 209-214, 2009. PMID: 19484437. DOI: 10.1007/s10384-009-0662-y
15 Coupland SE, Heimann H and Bechrakis NE: Primary intraocular lymphoma: A review of the clinical, histopathological and molecular biological features. Graefes Arch Clin Exp Ophthalmol *242(11)*: 901-913, 2004. PMID: 15565454. DOI: 10.1007/s00417-004-0973-0
16 Cheah CY, Milgrom S, Chihara D, Gombos DS, Pinnix CC, Dabaja BS and Fowler NH: Intensive chemoimmunotherapy and bilateral globe irradiation as initial therapy for primary intraocular lymphoma. Neuro Oncol *18(4)*: 575-581, 2016. PMID: 26487691. DOI: 10.1093/neuonc/nov253
17 Kaburaki T, Taoka K, Matsuda J, Yamashita H, Matsuda I, Tsuji H, Tanaka R, Nakazaki K, Nakamura F, Kamiya K, Kurokawa M, Ohtomo K and Aihara M: Combined intravitreal methotrexate and immunochemotherapy followed by reduced-dose whole-brain radiotherapy for newly diagnosed B-cell primary intraocular lymphoma. Br J Haematol *179(2)*: 246-255, 2017. PMID: 28699673. DOI: 10.1111/bjh.14848
18 Akiyama H, Takase H, Kubo F, Miki T, Yamamoto M, Tomita M, Mochizuki M, Miura O and Arai A: High-dose methotrexate following intravitreal methotrexate administration in preventing central nervous system involvement of primary intraocular lymphoma. Cancer Sci *107(10)*: 1458-1464, 2016. PMID: 27412324. DOI: 10.1111/cas.13012
19 Klimova A, Heissigerova J, Rihova E, Brichova M, Pytlik R, Spicka I, Mrazova K, Karolova J and Svozilkova P: Combined treatment of primary vitreoretinal lymphomas significantly prolongs the time to first relapse. Br J Ophthalmol *102(11)*: 1579-1585, 2018. PMID: 29378728. DOI: 10.1136/bjophthalmol-2017-311574
20 Fend F, Ferreri AJ and Coupland SE: How we diagnose and treat vitreoretinal lymphoma. Br J Haematol *173(5)*: 680-692, 2016. PMID: 27133587. DOI: 10.1111/bjh.14025
21 Smith JR, Pe'er J, Belfort RN, Cardoso F, Carvajal RD, Carvalho C, Coupland SE, Desjardins L, Francis JH, Gallie BL, Gombos DS, Grossniklaus HE, Heegaard S, Jager MJ, Kaliki S, Ksander BR, Maeurer M, Moreno E, Pulido JS, Ryll B, Singh AD, Zhao J, Parreira A, Wilson DJ and O'Brien JM: Proceedings of the association for research in vision and ophthalmology and champalimaud foundation ocular oncogenesis and oncology conference. Transl Vis Sci Technol *8(1)*: 9, 2018. PMID: 30652059. DOI: 10.1167/tvst.8.1.9
22 Bonzheim I, Giese S, Deuter C, Süsskind D, Zierhut M, Waizel M, Szurman P, Federmann B, Schmidt J, Quintanilla-Martinez L, Coupland SE, Bartz-Schmidt KU and Fend F: High frequency of MYD88 mutations in vitreoretinal B-cell lymphoma: A valuable tool to improve diagnostic yield of vitreous aspirates. Blood *126(1)*: 76-79, 2015. PMID: 25900979. DOI: 10.1182/blood-2015-01-620518
23 Miserocchi E, Ferreri AJM, Giuffrè C, Cangi MG, Francaviglia I, Calimeri T, Ponzoni M, Pecciarini L, Bandello FM and Modorati GM: MYD88 L265P mutation detection in the aqueous humor of patients with vitreoretinal lymphoma. Retina *39(4)*: 679-684, 2019. PMID: 30204732. DOI: 10.1097/IAE.0000000000002319

Received February 21, 2021
Revised March 29, 2021
Accepted April 2, 2021