

Original Article

Are there primary intraocular lymphomas that do not develop into central nervous system lymphomas?

Toshihiko Matsuo,^{1,2)} Takehiro Tanaka³⁾

Primary intraocular lymphomas frequently develop into central nervous system lymphomas and vice versa. This study reviewed 22 consecutive patients with primary intraocular lymphoma diagnosed by immunostaining of vitrectomy cell blocks, and examined whether they developed central nervous system lymphoma. Seventeen patients developed central nervous system lymphoma: 3 patients developed intraocular and central nervous system lymphoma simultaneously, 9 patients developed central nervous system lymphoma 1 month to 5 years (median, 3 months) after intraocular lymphoma, and 5 patients developed central nervous system lymphoma preceding the diagnosis of intraocular lymphoma by 3 months to 9 years and 8 months (median, 1.5 years). In contrast, 5 patients did not develop central nervous system lymphoma: 2 patients did not develop local recurrence or central nervous system lymphoma in the follow-up period of 5 years and 11 years, respectively, after vitrectomy alone without additional local or systemic treatment. The remaining 3 patients with intraocular lymphoma had insufficient follow-up periods to determine the prognosis. The results of CD5 immunostaining of vitrectomy specimens were found in pathology reports of 8 patients: 3 patients with CD5-positive large cells and 4 patients with CD5-negative large cells developed central nervous system lymphoma. In summary, only a small number of patients did not develop central nervous system lymphoma based on long-term follow-up after vitrectomy alone. CD5 was not a marker of central nervous system involvement in this study population.

Keywords: Intraocular lymphoma, central nervous system lymphoma, CD5, vitrectomy cell block, diffuse large B-cell lymphoma

INTRODUCTION

Primary intraocular lymphoma is classified together with primary central nervous system lymphoma,¹⁻⁴ and must be differentiated from secondary intraocular lymphoma, which is the infiltration of lymphoma developing outside of the central nervous system.⁵⁻⁷ Lymphoma in the eye manifests as vitreous opacity with or without infiltrative lesions in the sensory retina, subretinal pigment epithelium, or optic nerve.^{1,8} The diagnosis of lymphoma requires differential diagnosis from intraocular inflammatory diseases, namely, uveitis, which exhibit similar symptoms.⁹ The pathological diagnosis is carried out by immunostaining of paraffin sections of cell blocks obtained at vitrectomy for vitreous opacity.^{2,9}

Primary intraocular lymphoma frequently develops into central nervous system lymphoma simultaneously or subsequently at a different time point. Primary central nervous system lymphoma may be followed later by the diagnosis of intraocular lymphoma. The interval between the development

of intraocular lymphoma and central nervous system lymphoma varies over a long period of time.

We previously reported 11 consecutive patients with primary intraocular lymphoma.² In this study, we included 11 additional patients with primary intraocular lymphoma and assessed whether there are primary intraocular lymphomas that do not develop into central nervous system lymphoma during long-term follow-up. We also reviewed the results of CD5 immunostaining of large cells in vitrectomy cell blocks because CD5-positive diffuse large B-cell lymphoma is known for central nervous system infiltration.¹⁰

METHODS

This retrospective study included 22 consecutive patients with primary intraocular lymphoma who were diagnosed and followed between January 2005 and April 2019 (Table 1). The initial 11 patients were previously reported,² and their outcomes after May 2008 were further examined. The study

Received: May 28, 2019. Revised: August 15, 2019. Accepted: August 28, 2019. J-STAGE Advance Published: October 12, 2019
DOI:10.3960/jslr.19019

¹⁾Ophthalmology, Okayama University Hospital and Okayama University Medical School, ²⁾Okayama University Graduate School of Interdisciplinary Science and Engineering in Health Systems, ³⁾Pathology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences

Corresponding author: Toshihiko Matsuo, MD, PhD, Regenerative and Reconstructive Medicine (Ophthalmology), Okayama University Graduate School of Interdisciplinary Science and Engineering in Health Systems, Shikatacho 2-5-1, Okayama City 700-8558, Japan. E-mail: matsuo@cc.okayama-u.ac.jp

Copyright © 2019 The Japanese Society for Lymphoreticular Tissue Research


 This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Table 1. Clinical features of the 22 consecutive patients with primary intraocular lymphoma

Case	*Age/Sex	Follow-up period	Laterality	Retinal lesion	Vitreous opacity	Vitreotomy	CD5 in vitrectomy sample	Brain lesion	#Onset of brain lesion	Treatment and outcome
1	68/Male	4 yr 2 mo	Right eye	No	Yes	Yes	n.d.	Yes	simultaneous	Chemotherapy Died of brain lymphoma
			Left eye	No	Yes	Yes	n.d.			
2	72/Male	2 yr 4 mo	Right eye	No	Yes	Yes	n.d.	Yes	1 mo later	Chemotherapy Died of brain lymphoma
			Left eye	Yes	Yes	Yes	n.d.			
3	68/Male	7 mo	Right eye	No	Yes	Yes	n.d.	No		No additional treatment Renal dialysis after nephritis for past 4 yr Died of renal failure
			Left eye	No	Yes	Yes	n.d.			
4	74/Female	2 yr 10 mo	Right eye	Yes	Yes	Yes	n.d.	Yes	3 mo previously	Chemotherapy Brain radiation Alive at final follow-up, lost thereafter
			Left eye	No	No	No				
5	72/Female	5 yr 8 mo	Right eye	No	Yes	Yes	n.d.	No		No additional treatment Left sphenoid ridge to orbital meningioma 26 yr previously Died of other causes
			Left eye	Unknown						
6	69/Female	5 yr 8 mo	Right eye	No	Yes	Yes	n.d.	Yes	1 yr 10 mo previously	Chemotherapy Died of brain lymphoma
			Left eye	No	Yes	Yes	n.d.			
7	76/Male	2 yr 4 mo	Right eye	Yes	Yes	Yes	n.d.	Yes	10 mo previously	Chemotherapy Brain radiation (40 Gy) Alive at final follow-up, lost thereafter
			Left eye	Yes	Yes	Yes	n.d.			
8	70/Female	2 yr 1 mo	Right eye	No	Yes	Yes	Negative	Yes	1 mo later	Chemotherapy Died of brain lymphoma
			Left eye	No	No	No				
9	74/Female	1 yr 7 mo	Right eye	No	Yes	Yes	n.d.	Yes	11 mo later	Chemotherapy Died of brain lymphoma
			Left eye	Yes	Yes	Yes	n.d.			
10	79/Female	8 mo	Right eye	Yes	Yes	Yes	n.d.	No		Right eye radiation (40 Gy) Died of pancytopenia
			Left eye	No	No	No				
11	82/Female	11 yr	Right eye	No	No	No		No		No additional treatment Alive at last visit
			Left eye	No	Yes	Yes	n.d.			
12	84/Female	10 mo	Right eye	No	Yes	Yes	Positive	Yes	3 mo later	Chemotherapy Died of brain lymphoma
			Left eye	No	Yes	Yes	Positive			
13	42/Female	7 yr 2 mo	Right eye	No	Yes	Yes	n.d.	Yes	5 yr later	Vitreous MTX in both eyes at other hospital Prophylactic systemic MTX & Ara-C AutoPBSCT 5 yr later Alive at last visit
			Left eye	No	Yes	Yes	n.d.			
14	74/Male	9 mo	Right eye	No	No	No		Yes	1 mo later	Chemotherapy Died of brain lymphoma
			Left eye	Yes	Yes	Yes	Negative			
15	64/Male	6 yr 5 mo	Right eye	No	Yes	Yes	n.d.	Yes	1.5 yr previously	Chemotherapy AutoPBSCT 1.5 yr previously Brain & both eyes radiation 2 yr later Alive at last visit
			Left eye	No	Yes	Yes	n.d.			
16	73/Female	6 yr 4 mo	Right eye	No	No	No	n.d.	Yes	4.5 yr later	Chemotherapy 4.5 yr later Alive at last visit
			Left eye	No	Yes	Yes	n.d.			

17	81/Female	5 mo	Right eye	No	No	No	n.d.	Yes	simultaneous	Brain radiation Died of brain lymphoma
			Left eye	No	Yes	Yes	n.d.			
18	68/Female	2 yr 10 mo	Right eye	No	Yes	Yes	Positive	Yes	5 mo later	Chemotherapy 5 mo later Brain radiation 2 yr later Died of brain lymphoma
			Left eye	No	Yes	Yes	Positive			
19	70/Male	1 yr 3 mo	Right eye	No	Yes	Yes	Negative	Yes	simultaneous	Chemotherapy, Brain radiation Died of brain lymphoma
			Left eye	No	No	No				
20	63/Female	4 yr 8 mo	Right eye	No	Yes	Yes	Negative	Yes	2 mo later	Chemotherapy, autoPBSCT 2nd autoPBSCT 3 yr later Died of brain lymphoma
			Left eye	No	Yes	Yes	Negative			
21	76/Female	3 yr	Right eye	No	Yes	Yes	Negative	No		Chemotherapy Both eyes radiation 2 yr 5 mo later Left eye lesion and vitrectomy 2 yr 4 mo later Alive at last visit
			Left eye	No	Yes	Yes	Negative			
22	69/Male	3 yr	Right eye	No	Yes	Yes	Positive	Yes	9 yr and 8 mo previously	Systemic MTX and brain radiation previously at other hospital Right eye recurrence at initial visit Right eye radiation and systemic MTX 1 yr later Alive at last visit
			Left eye	No	No	No				

*Age (years) at initial visit for eye examination. #Onset of brain lesion relative to the onset of eye manifestations. "Later" or "previously" relative to initial visit to ophthalmology department. Chemotherapy indicates systemic chemotherapy (usually R-CHOP with or without methotrexate) and brain radiation indicates whole-brain radiation. Systemic MTX indicates high-dose MTX. "Last visit" was in April 2019. Abbreviations are: n.d., not described; yr, years; mo, months, MTX, methotrexate; Ara-C, cytarabine; autoPBSCT, autologous peripheral blood stem cell transplantation.

was performed according to the Declaration of Helsinki and was approved as a retrospective study by the ethics committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and Okayama University Hospital. All 22 patients underwent vitreous surgery (vitrectomy) for vitreous opacity by a single surgeon (TM) at Okayama University Hospital, and were diagnosed with large B-cell lymphoma by immunostaining of paraffin sections of vitrectomy cell blocks at the pathology department.^{2,9}

Vitrectomy fluid in two or more 50-mL disposable tubes was mixed with one-tenth the volume of 4% paraformaldehyde and centrifuged for 20 minutes at 3000 revolutions per minute (rpm) at room temperature. The pellet in each tube was suspended in a small volume of 4% paraformaldehyde, combined in one 15-mL disposable tube, and centrifuged for 15 minutes at 3000 rpm at room temperature.^{2,9} The final pellet was embedded in paraffin, and sections were cut and stained by hematoxylin-eosin. Immunohistochemical staining was based on the protocol recommended for the Bond Polymer Refine Detection Kit in the system of Bond-III Fully Automated IHC and ISH Stainer (Leica Biosystems, Welzlar, Germany). Primary antibodies used were: mouse monoclonal antibodies against CD3 (LN10 clone, 1:200 dilution), CD5 (4C7 clone, 1:100 dilution), CD20 (L26 clone, 1:150 dilution), and Ki67 (MM1 clone, 1:200 dilution, Leica Biosystems Novocastra). The pathological diagnosis was based on large cells with anomalous nuclei on hematoxylin-eosin

staining being positive for CD20 and Ki67, but negative for CD3. The Ki67 labeling index was set at 50% or higher.

RESULTS

The 22 consecutive patients were 14 women and 8 men, with the age at initial visit for eye examinations ranging from 42 to 84 years (median, 71 years). The follow-up period ranged from 5 months to 11 years (median, 2 years and 10 months). Both eyes were affected by the intraocular lymphoma in 12 patients, whereas only the right eye or left eye was involved in 6 patients and 4 patients, respectively. Regarding treatments, systemic chemotherapy was performed for 8 patients, whole brain radiation after systemic chemotherapy for 4 patients, autologous peripheral blood stem cell transplantation after chemotherapy for 3 patients, whole brain radiation for one patient, chemotherapy with eye radiation for 2 patients, eye radiation for one patient, and no treatment for 3 patients (Table 1).

Of the 22 patients with primary intraocular lymphoma (Table 1), 17 developed central nervous system lymphoma: 3 patients developed intraocular and central nervous system lymphoma simultaneously, 9 patients developed central nervous system lymphoma 1 month to 5 years (median, 3 months) after the development of intraocular lymphoma, and 5 patients developed central nervous system lymphoma preceding the diagnosis of intraocular lymphoma by 3 months to 9 years and 8 months (median, 1 years and 6 months).

In contrast, the other 5 patients did not develop central nervous system lymphoma during the follow-up period. Of these 5 patients, 3 had an insufficient follow-up period after the diagnosis of primary intraocular lymphoma. One patient (Case 3) who was on renal dialysis for 4 years before diagnosis died of renal failure approximately half a year after the diagnosis of primary intraocular lymphoma, and the other patient (Case 10) died approximately half a year after right eye radiation for the recurrent intraocular lesion. These 2 patients

did not undergo systemic chemotherapy. The third patient (Case 21, Fig. 1) developed primary intraocular lymphoma first in the right eye and underwent prophylactic systemic chemotherapy even though magnetic resonance imaging demonstrated no brain lesion. She developed intraocular lymphoma in the left eye approximately 2.5 years later, and underwent prophylactic radiotherapy for both eyes even though local recurrence was not observed in either eye. She was followed further for half a year and was alive at the last

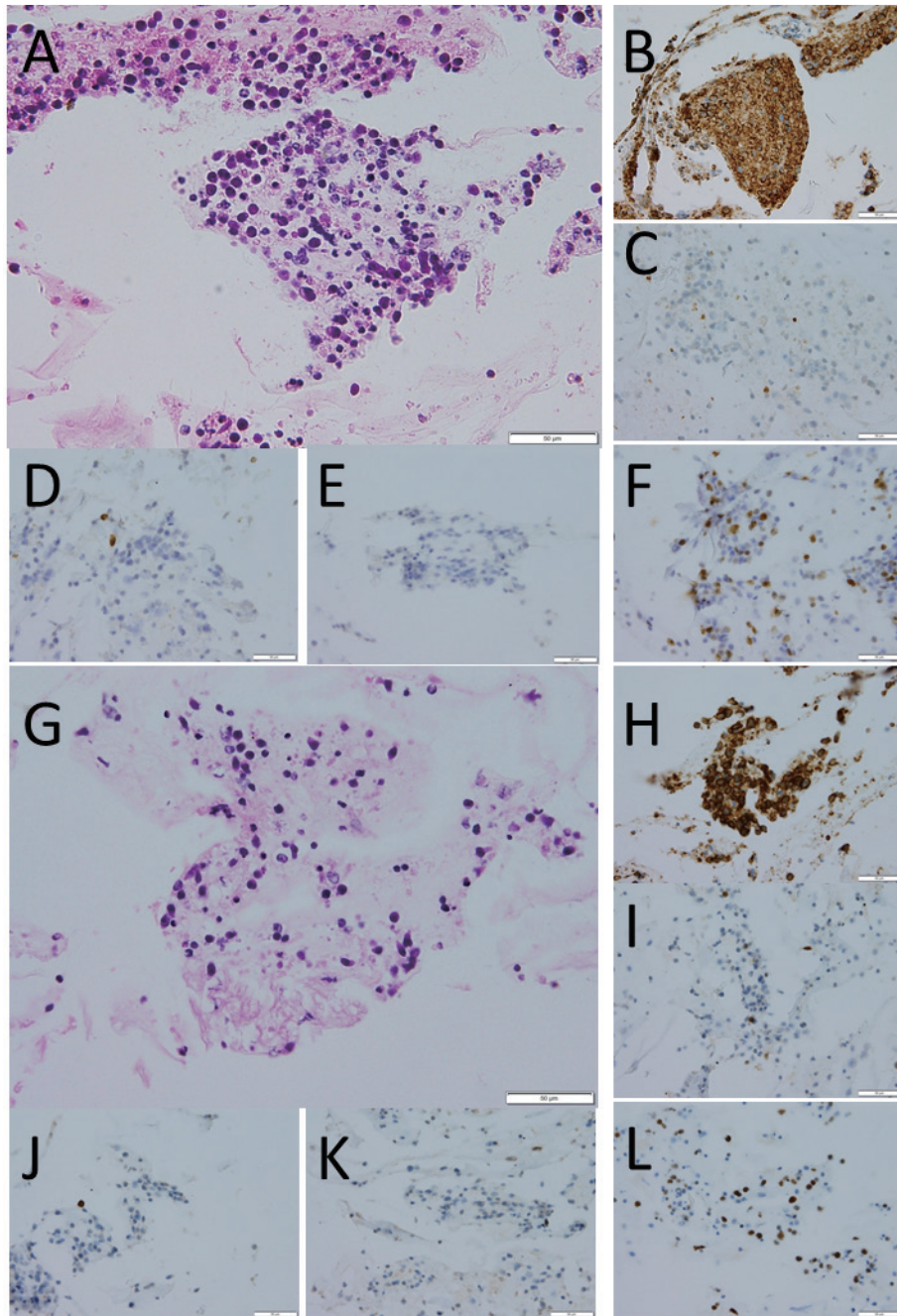


Fig. 1. Case 21. Top, right eye. Bottom, left eye. A 76-year-old woman developed primary intraocular lymphoma in the right eye (top) and underwent prophylactic systemic chemotherapy. She developed primary intraocular lymphoma in the left eye (bottom) 2.5 years later and then underwent radiation for both eyes. Large cells (*A, G*) in vitrectomy cell blocks are positive for CD20 (*B, H*) and Ki67 (*F, L*), but negative for CD3 (*C, I*), CD5 (*D, J*), and CD10 (*E, K*). White bar = 50 μ m.

visit for this study.

The fourth patient (Case 5, Fig. 2, top) had been followed up for 5 years until death by other causes after the diagnosis of primary intraocular lymphoma. The fifth patient (Case 11, Fig. 2, bottom) had been followed up for 11 years after the diagnosis of primary intraocular lymphoma and was alive at the last visit for this study. These 2 patients did not undergo additional local or systemic chemotherapy, or radia-

tion of the eye.

The results of CD5 immunostaining of vitrectomy specimens in the pathology reports were found for 8 of the 22 consecutive patients with primary intraocular lymphoma: 3 patients had CD5-positive large cells, whereas 5 had CD5-negative large cells (Table 1). Four patients had the vitreous of both eyes examined: 2 patients had CD5-positive large cells, whereas the other 2 had CD5-negative large cells in the

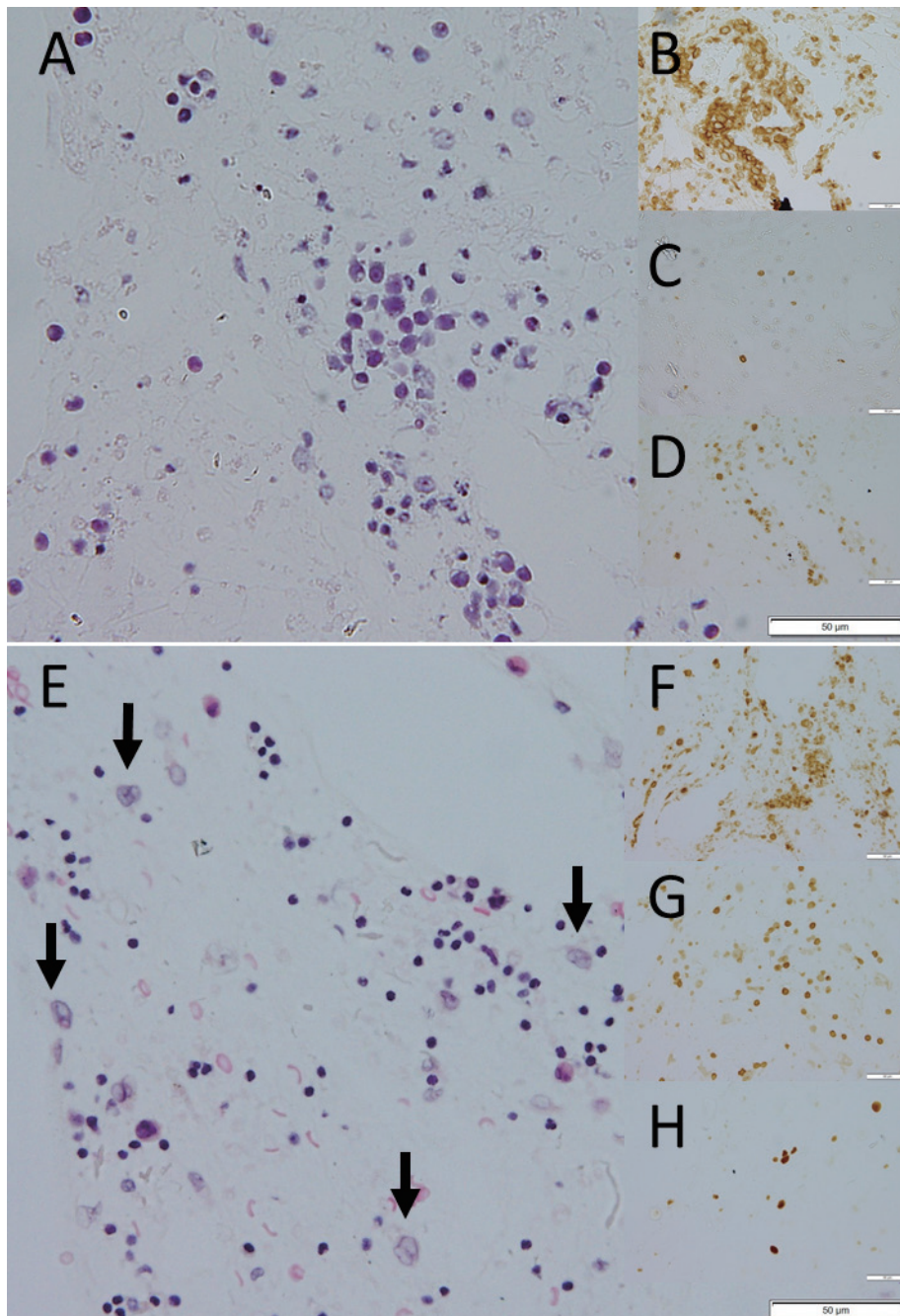


Fig. 2. Top. Case 5. A 72-year-old woman was alive for 5 years after the diagnosis of primary intraocular lymphoma in the right eye and died of other causes. Large cells (**A**) in the vitrectomy cell block are positive for CD20 (**B**) and Ki67 (**D**), but negative for CD3 (**C**). Bottom. Case 11. An 82-year-old woman was alive at the last visit for this study 11 years after the diagnosis of primary intraocular lymphoma in the left eye. Large cells (arrows in **E**) in the vitrectomy cell block are positive for CD20 (**F**) and Ki67 (**H**), but negative for CD3 (**G**). CD3-positive T cells are also present (**G**). White bar = 50 μ m.

vitreous of both eyes. The 3 patients with CD5-positive large cells and 4 patients with CD5-negative large cells in the vitreous of one or both eyes developed central nervous system lymphoma. Only one patient (Case 21, Fig. 1) with CD5-negative large cells in the vitreous of both eyes did not develop central nervous system lymphoma during the short-term follow-up of half a year until the last visit for this study.

DISCUSSION

Primary intraocular lymphoma naturally has a good prognosis if it does not develop into central nervous system lymphoma. The goals of this study were to find patients with primary intraocular lymphoma who did not develop central nervous system lymphoma during follow-up, and to examine whether CD5-positive large cells in vitrectomy specimens are a marker of central nervous system lymphoma.

CD5-positive diffuse large B-cell lymphoma was known to have a poor prognosis due to the higher incidence of central nervous system infiltration.¹⁰ In contrast, large B-cells in primary intraocular lymphoma were found to be CD5-negative by flow cytometry analysis of vitrectomy specimens.¹¹ To the best of our knowledge, there is only one case report describing CD5-positive abnormal cells in vitreous specimens by flow cytometry.¹² In the present study, we revealed CD5-positive large cells and CD5-negative large cells by immunostaining in the sections of vitrectomy cell blocks from the series of patients with primary intraocular lymphoma. However, CD5-positive or -negative large B-cells in vitrectomy specimens of primary intraocular lymphoma cannot be used as a marker of the development of central nervous system lymphoma. No further evidence of the origin of lymphoma cells, such as *myc* expression or translocation, was available in the present study.

Most patients with central nervous system lymphoma died of the disease. It should be noted that one young patient (Case 13) developed primary intraocular lymphoma in both eyes at the age of 42, and immediately underwent prophylactic systemic chemotherapy using methotrexate and cytarabine. She also received intravitreal injection of methotrexate at another hospital before systemic chemotherapy. However, 5 years later, she developed a brain lesion and underwent autologous peripheral blood stem cell transplantation as a standard treatment option.¹³⁻¹⁵ She was well for the following 2 years until the last visit for this study.

As shown by the course of this patient (Case 13), there is no established standard treatment strategy for primary intraocular lymphoma. In addition, it remains controversial whether prophylactic treatment, systemic chemotherapy or radiotherapy to the eye or brain, can prevent future brain lesions, thereby improving the survival of patients with primary intraocular lymphoma.¹⁶⁻¹⁸ It also remains unknown whether intravitreal methotrexate injection after vitrectomy for primary intraocular lymphoma plays a role in preventing central nervous system lymphoma.¹⁸⁻²⁰

At our hospital, intravitreal methotrexate injection is not performed for patients with primary intraocular lymphoma

because it is not approved by health insurance in Japan. In the present series of 22 patients, only 2 (Case 10 and Case 22) developed local recurrence in the eye after vitrectomy and underwent whole eye radiation. The other 20 patients did not exhibit local recurrence in the eye after vitrectomy alone. It should be noted that 2 patients (Case 5 and Case 11, Fig. 2) with primary intraocular lymphoma after vitrectomy alone did not develop local recurrence in the eye or central nervous system lymphoma during long-term follow-up.

In conclusion, a small number of patients with primary intraocular lymphoma did not develop central nervous system lymphoma after vitrectomy alone without additional local or systemic treatment. At present, there is no marker available to predict whether a patient with primary intraocular lymphoma will develop central nervous system lymphoma.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in this study.

REFERENCES

- 1 Matsuo T, Yamaoka A, Shiraga F, Matsuo N. Two types of initial ocular manifestations in intraocular-central nervous system lymphoma. *Retina*. 1998; 18 : 301-307.
- 2 Matsuo T, Ichimura K, Ichikawa T, *et al*. Positron emission tomography/computed tomography after immunocytochemical and clonal diagnosis of intraocular lymphoma with vitrectomy cell blocks. *J Clin Exp Hematop*. 2009; 49 : 77-87.
- 3 Sagoo MS, Mehta H, Swampillai AJ, *et al*. Primary intraocular lymphoma. *Surv Ophthalmol*. 2014; 59 : 503-516.
- 4 Tang LJ, Gu CL, Zhang P. Intraocular lymphoma. *Int J Ophthalmol*. 2017; 10 : 1301-1307.
- 5 Karakawa A, Taoka K, Kaburaki T, *et al*. Clinical features and outcomes of secondary intraocular lymphoma. *Br J Haematol*. 2018; 183 : 668-671.
- 6 Matsuo T, Tanaka T, Ichimura K, Meguri Y. Intraocular relapse with hypopyon and retinal infiltrates after chemotherapy and peripheral blood stem cell transplantation for extranodal NK/T-cell lymphoma. *J Clin Exp Hematop*. 2015; 55 : 157-161.
- 7 Matsuo T, Tanaka T, Yano T. Intraocular lymphoma as relapse after chemotherapy for primary breast diffuse large B-cell lymphoma. *J Clin Exp Hematop*. 2018; 58 : 180-183.
- 8 Abu Samra K, Oray M, Ebrahimiadib N, *et al*. Intraocular lymphoma: descriptive data of 26 patients including clinico-pathologic features, vitreous findings, and treatment outcomes. *Ocul Immunol Inflamm*. 2018; 26 : 347-352.
- 9 Matsuo T, Ichimura K. Immunocytochemical diagnosis as inflammation by vitrectomy cell blocks in patients with vitreous opacity. *Ophthalmology*. 2012; 119 : 827-837.
- 10 Miyazaki K, Yamaguchi M, Suzuki R, *et al*. CD5-positive diffuse large B-cell lymphoma: a retrospective study in 337 patients treated by chemotherapy with or without rituximab. *Ann Oncol*. 2011; 22 : 1601-1607.
- 11 Raparia K, Chang CC, Chévez-Barrios P. Intraocular lymphoma:

- diagnostic approach and immunophenotypic findings in vitrectomy specimens. *Arch Pathol Lab Med.* 2009; 133 : 1233-1237.
- 12 Nagata K, Inaba T, Kinoshita S. CD5-positive primary intraocular B-cell lymphoma arising during methotrexate and tumor necrosis factor inhibitor treatment. *Case Rep Ophthalmol.* 2015; 6 : 301-306.
 - 13 Ferreri AJ, Illerhaus G. The role of autologous stem cell transplantation in primary central nervous system lymphoma. *Blood.* 2016; 127 : 1642-1649.
 - 14 Kassam S, Chernucha E, O'Neill A, *et al.* High-dose chemotherapy and autologous stem cell transplantation for primary central nervous system lymphoma: a multi-centre retrospective analysis from the United Kingdom. *Bone Marrow Transplant.* 2017; 52 : 1268-1272.
 - 15 Kasenda B, Ihorst G, Schroers R, *et al.* High-dose chemotherapy with autologous haematopoietic stem cell support for relapsed or refractory primary CNS lymphoma: a prospective multicentre trial by the German Cooperative PCNSL study group. *Leukemia.* 2017; 31 : 2623-2629.
 - 16 Guirguis HR, Cheung MC, Mahrous M, *et al.* Impact of central nervous system (CNS) prophylaxis on the incidence and risk factors for CNS relapse in patients with diffuse large B-cell lymphoma treated in the rituximab era: a single centre experience and review of the literature. *Br J Haematol.* 2012; 159 : 39-49.
 - 17 Zahid MF, Khan N, Hashmi SK, Kizilbash SH, Barta SK. Central nervous system prophylaxis in diffuse large B-cell lymphoma. *Eur J Haematol.* 2016; 97 : 108-120.
 - 18 Ma WL, Hou HA, Hsu YJ, *et al.* Clinical outcomes of primary intraocular lymphoma patients treated with front-line systemic high-dose methotrexate and intravitreal methotrexate injection. *Ann Hematol.* 2016; 95 : 593-601.
 - 19 Akiyama H, Takase H, Kubo F, *et al.* High-dose methotrexate following intravitreal methotrexate administration in preventing central nervous system involvement of primary intraocular lymphoma. *Cancer Sci.* 2016; 107 : 1458-1464.
 - 20 Kaburaki T, Taoka K, Matsuda J, *et al.* Combined intravitreal methotrexate and immunochemotherapy followed by reduced-dose whole-brain radiotherapy for newly diagnosed B-cell primary intraocular lymphoma. *Br J Haematol.* 2017; 179 : 246-255.