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CLINICAL INVESTIGATION

Clinical features and diagnostic significance of the intraocular fluid of 217 patients with intraocular lymphoma

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Abstract
Purpose Intraocular lymphoma is a rare disease with a poor prognosis. Early diagnosis and early treatment greatly influence the survival prognosis of this disease. This retrospective study aimed to clarify the clinical features of patients diagnosed with intraocular lymphoma, and the diagnostic significance of results from analysis of vitreous samples including cytology, cytokine measurements, and the IgH gene rearrangement test.
Methods We reviewed 217 patients with intraocular lymphoma diagnosed at 25 medical institutions in Japan. Together with clinical observation, cytological analysis, determination of the levels of cytokines, and/or detection of IgH gene rearrangements were conducted using vitreous fluid specimens. The results were studied in conjunction with clinical findings of intraocular lymphoma. Survival curves were estimated by use of the Kaplan–Meier method.
Results The subjects comprised 85 men and 132 women, with a mean age at first ophthalmological examination of 63.4 years. The mean observation period was 41.3 months. During the observation period, 69 patients had onset of lymphoma in one eye and 148 had onset in both eyes. Intraocular lymphoma with involvement of the central nervous system (CNS) was most common, found in 60.8 % of the patients, whereas intraocular lymphoma without involvement of other organs was found in 28.1 % of patients. With respect to onset patterns, 82.5 % of patients developed primary ocular lesions whereas 16.1 % developed primary CNS lesions preceding intraocular lymphoma. Blurred vision and ataxia were the most common ocular and extra-ocular symptoms that prompted patients to seek medical examination. Vitreous opacification was the most common ocular finding. The detection rates of malignant cytology, IL-10/IL-6 ratio greater than 1.0, and IgH gene rearrangements in vitreous specimens were 44.5, 91.7, and 80.6 %, respectively, of patients tested. IL-10/IL-6 ratio greater than 1.0 had the highest overall detection rate, and was extremely high (≥90 %) in patients with or without vitreous opacification. The 5-year survival rate was 61.1 %.
Conclusion Cytokine analysis of vitreous biopsy had the highest detection rate for intraocular lymphoma. This supplementary diagnostic test should be performed frequently to confirm a diagnosis of intraocular lymphoma.

Keywords Intraocular lymphoma · Clinical features · Multicenter study

Introduction

Most intraocular lymphomas are non-Hodgkin's lymphomas. Given that intraocular lymphoma represents 1 % of non-Hodgkin's lymphomas, less than 1 % of intraocular tumors [1], or 1 % of intraocular inflammation [2], it is extremely rare. A definitive diagnosis requires cytological examination confirming that the intraocular fluid or tissue contains large atypical lymphoid cells with large and irregular nuclei and prominent nucleoli. However, cytodiagnosis can also be difficult because of the effect of systemic corticosteroids administered because of misdiagnosis of intraocular inflammation [3, 4], loss of tumor cells by perfusion, and damage to tumor cells by a vitrectomy cutter during surgery [5]. Therefore, several supplementary diagnostic methods, for example cytokine analysis to

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determine the ratio of interleukin (IL)-10 to IL-6 (IL-10/IL-6 ratio) [6], molecular analysis to detect immunoglobulin heavy chain (IgH) gene rearrangements to confirm monoclonality [7–9], genetic analysis [10], and flow cytometry for B cell phenotype [11] are currently used to support the clinical findings in the diagnosis of intraocular lymphoma.

Some intraocular lymphoma patients manifest ocular symptoms only and have relatively good prognosis. However, 60–90 % of primary intraocular lymphoma patients develop central nervous system (CNS) lymphoma [7, 12] with a poor survival prognosis, suggesting the need for careful observation. Freeman et al. [13] reported in 1987 that the 5-year survival rate in 32 cases of intraocular lymphoma (including 18 cases of intraocular lymphoma with CNS involvement) was slightly lower than 30 %. Given that early diagnosis and treatment are the principles of cancer therapy, general ophthalmologists should be aware of the clinical features of intraocular lymphoma.

Although intraocular lymphoma is receiving increasing attention following recent reports that reviewed a large number of cases in Europe and North America [14–16], no studies examined a large number of patients among Asian populations. Consequently, not all of the features of intraocular lymphoma have been clarified.

In this multicenter study, we investigated the clinical features of intraocular lymphoma in 217 patients, who were followed at 25 medical institutes in Japan. We present the clinical features identified, and discuss the diagnostic criteria and the significance of vitreous sample analyses including cytology, cytokine measurement, and IgH gene rearrangement testing.

Patients and methods

A questionnaire was sent to departments of ophthalmology in hospitals throughout Japan to obtain information on patient characteristics, clinical features (initial symptoms and ocular findings), and diagnostic vitrectomy (cytological findings, cytokine analysis results, and molecular analysis results). Data of 217 patients provided by 25 departments were retrospectively analyzed. There were no patients who were immunocompromised, HIV-positive, or had T-cell lymphoma. Metastatic intraocular lymphoma associated with systemic lymphoma was excluded. Institutional review board approval was obtained for this retrospective study. Vitreous biopsy and its purpose were explained and informed consent was obtained from the patients and their families.

All patients with primary ocular lesions were examined by cranial magnetic resonance imaging (MRI) and/or computed tomography (CT) to detect CNS involvement during the follow-up period. Systemic work-up was basically performed by use of scintigraphy (gallium scintigraphy and/or positron emission tomography) and/or contrast enhanced CT.

Diagnostic vitrectomy was performed using a 3-port pars plana 20, 23 or 25-gauge vitrectomy technique. Basically, vitreous samples were collected by use of a vitreous cutter during vitrectomy. The samples were centrifuged, the concentrated cells were submitted for histopathological examination, and the supernatant was assayed for cytokine levels. Additional vitreous specimens obtained by use of a vitreous cutter were submitted for analysis of IgH gene rearrangement. Cytological preparations were reviewed at each participating institution by an experienced cytopathologist. The following classifications were used for cytological analysis. Negative is the absence of typical, or presence of abnormal cells or atypical cytology but no evidence of malignancy. Suspicious is cytology suggestive, but not conclusive of malignancy. Positive is cytology strongly suggestive of malignancy or cytology conclusive for malignancy. Levels of cytokines IL-10 and IL-6 were measured by enzyme-linked immunosorbent assay (ELISA) or chemiluminescent enzyme immunoassay (CLEIA). An IL-10/IL-6 ratio greater than 1.0 was judged to be useful as a supplementary diagnostic criterion. Molecular analysis involved polymerase chain reaction (PCR) to determine gene rearrangements in the variable region of the immunoglobulin heavy chain. DNA was extracted from fresh biopsies.

For statistical analysis, the Wilcoxon signed rank sum test was performed. Overall survival was defined as the time between first medical examination and subsequent endpoints or death. Survival curves were estimated by use of the Kaplan–Meier method. A p value of less than 0.05 was considered statistically significant. All statistical analysis was performed by use of MedCalc statistical software (MedCalc Software, Mariakerke, Belgium).

Results

The 217 subjects (85 men and 132 women) had a mean age at first medical examination of 63.4 years (range 35–90 years), 62.0 (35–88) years for the men and 64.4 (38–90) years for the women. The mean observation period was 41.3 months (range 3 months–13 years 5 months) during the survey period from July 1988 to January 2009. The initial ocular symptoms that prompted patients to visit an ophthalmology clinic were, in descending order, blurred vision or reduced vision (157, 72.4 %), floater symptom (48, 22.1 %), visual field disturbance (5, 2.3 %), and abnormal ocular findings in a periodic medical examination (3, 1.4 %) (Table 1). The most common initial subjective

Table 1 Initial subjective ocular symptoms

Symptoms	Total (%)
Blurred or reduced vision	157 (72.4)
Floater symptom	48 (22.1)
Visual field disturbance	5 (2.3)
Diagnosed by periodic inspection	3 (1.4)
Others	4 (1.8)

Table 2 Initial subjective extra-ocular symptoms

Symptoms	Total (%)
Ataxia	10 (4.6)
Dizziness	4 (1.8)
Headache	4 (1.8)
Disorientation	3 (1.4)
Others	6 (2.8)

extra-ocular symptom was ataxia (10, 4.6 %), followed by dizziness (4, 1.8 %), headache (4, 1.8 %), and disorientation (3, 1.4 %) (Table 2). During the observation period, 69 of the 217 patients (31.8 %) had onset in one eye and 148 patients (68.2 %) had onset in both eyes. Vitreous opacification was the most common initial ocular finding, found in 197 of the patients (90.8 %); this was followed by subretinal infiltration in 124 cases (57.1 %), iritis in 68 cases (31.3 %), keratic precipitates in 54 cases (24.9 %), retinal vasculitis in 21 cases (9.7 %), secondary glaucoma in 9 cases (4.1 %), retinal hemorrhage in 5 cases (2.3 %), optic disc swelling in 4 cases (1.8 %), vitreous hemorrhage in 3 cases (1.4 %), retinal exudate in 3 cases (1.4 %), complicated cataract in 2 cases (0.9 %), and retinal detachment in 2 cases (0.9 %). Subconjunctival mass, scleritis, hypopyon, and proliferative retinopathy were less common initial findings, and were found in one case each (0.5 %) (Table 3).

Of the 217 patients, 132 (60.8 %) manifested both ocular and CNS lesions during the observation period whereas 61 patients (28.1 %) manifested ocular lesions only. Eleven patients (5.1 %) had involvement of both the CNS and other organs. Other organs involved in these cases were the paranasal sinuses in 3 cases, the neck and systemic lymph nodes in 2 cases, the testis in 2 cases, and others in 5 cases (overlapping). Ten patients (4.6 %) had involvement of organs other than the CNS. The organs involved in these cases were the neck and abdomen lymph nodes in 4 cases, the small intestine in 2 cases and others in 5 cases (overlapping) (Table 4).

One-hundred and seventy-nine patients (82.5 %), including 61 with ocular symptoms only, developed ocular lesion(s) first. Thirty-five patients (16.1 %) developed CNS lesions before onset of the ocular lesion. Three patients

Table 3 Ocular findings of intraocular lymphoma

Ocular findings	Total (%)
Vitreous opacification	197 (90.8)
Subretinal infiltration	124 (57.1)
Iritis	68 (31.3)
Keratic precipitates	54 (24.9)
Retinal vasculitis	21 (9.7)
Secondary glaucoma	9 (4.1)
Retinal hemorrhage	5 (2.3)
Optic disc swelling	4 (1.8)
Vitreous hemorrhage	3 (1.4)
Retinal exudate	3 (1.4)
Complicated cataract	2 (0.9)
Retinal detachment	2 (0.9)
Subconjunctival mass	1 (0.5)
Scleritis	1 (0.5)
Hypopyon	1 (0.5)
Proliferative vitreous retinopathy	1 (0.5)

Table 4 Organ involvement in patients with intraocular lymphoma

Organ involvement	Total (%)
Eye and CNS	132 (60.8)
Eye only	61 (28.1)
Eye, CNS, and systemic	11 (5.1)
Eye and systemic	10 (4.6)
Detail unknown	3 (1.4)

Table 5 Onset pattern of intraocular lymphoma

Onset pattern	Total (%)
Primary intraocular lymphoma	179 (82.5)
Primary CNS lymphoma	35 (16.1)
Eye and CNS simultaneously	3 (1.4)

(1.4 %) had simultaneous onset in the eye(s) and CNS (Table 5).

The average interval between the onset of primary ocular lesion and of the secondary CNS lesions was 21.7 months (range 1 week–10 years) in 106 cases, whereas that between the onset of primary CNS lesions and of secondary ocular lesions was 12.5 months (range 1 month–5 years) in 31 cases. Statistical analysis using the Wilcoxon signed rank sum test revealed a significant difference between these results.

Examinations of vitreous fluid specimens revealed that the rate of positive cytology for malignancy was 44.5 % in 164 of the cases tested. The detection rate of IL-10/IL-6 ratio greater than 1.0 was 91.7 % in 145 cases, whereas that

Table 6 Positive rates of diagnostic tests conducted on vitreous biopsy

Diagnostic test	% (*n*)
Cytological examination	44.5 (164)
IL-10/IL-6 ratio >1.0	91.7 (145)
Gene rearrangement	80.6 (67)

Positive rate = number of positive cases/total number of cases examined (*n*)

Table 7 Relationship between vitreous opacification and vitreous biopsy results

Diagnostic tests	Vitreous opacity	
	Present % (*n*)	Absent % (*n*)
Cytological examination	47.1 (153)	10.0 (10)
IL-10/IL-6 ratio >1.0	91.7 (133)	90.9 (11)
Gene rearrangement	80.6 (62)	75.5 (4)

Positive rate = number of positive cases/total number of cases examined (*n*)

of IgH gene rearrangements was 80.6 % in 67 cases (Table 6). Among the 52 cases in which all three examinations were performed, 19.2 % (10 cases) tested positive for all three, 55.8 % (29 cases) for two, and 21.2 % (11 cases) for one; 3.8 % (2 cases) were negative for all three. The 52 cases included 15 without any involvement of other organs, 30 with the involvement of the CNS, 4 with the involvement of other organs, and 3 with no relevant information. The two patients tested negative for all three had primary CNS lymphoma, and were treated with high-dose methotrexate and whole-brain radiotherapy before diagnosis of intraocular lesion.

We further examined whether detection rates in the above three examinations were different between the patients with clinically detectable vitreous opacification and those without. The detection rates of positive cytology for malignancy were 47.1 % in 153 of the patients with vitreous opacification and 10.0 % in 10 patients without. The detection rate of IgH gene rearrangements was also higher in 62 of the patients with vitreous opacification (80.6 %) compared with the 4 patients without (75.0 %). However, the detection rates of the IL-10/IL-6 ratio greater than 1.0 were similarly high in 133 of the patients with vitreous opacification (91.7 %) and in 11 patients without (90.9 %) (Table 7).

The average interval between the occurrence of subjective symptoms and definitive diagnosis as intraocular lymphoma was 10.9 months (range 2 weeks to 9 years). The average interval required for definitive diagnosis from the occurrence of subjective symptoms was 12.8 months (1 month–9 years) in the 173 patients who had primary ocular lesions, 4.6 months (2 weeks–17 months) in the 24 patients who had primary lesions in the CNS, 3.8 months (2 weeks–11 months) in the patients who had primary lesions in the other organs, and 10.7 months (9 weeks–14 months) in the patients who had primary lesions in both eyes and CNS involvement. The time interval required for a definitive diagnosis was significantly longer for those patients who had developed primary ocular lesions than for those who had primary lesions in other organs (Wilcoxon signed rank sum test, $p < 0.05$).

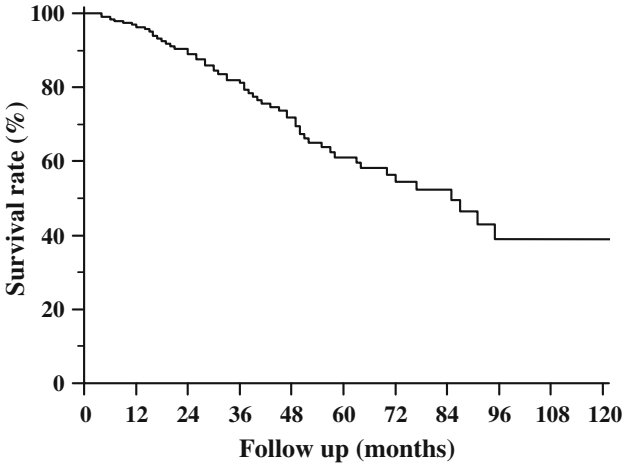

Fig. 1 Overall survival curve for 195 identified intraocular lymphoma patients both dead or alive

For the 195 intraocular lymphoma patients, either dead or alive, identified at the following endpoints, the 5-year survival rate was 61.1 % (Fig. 1).

Discussion

The first case of intraocular lymphoma was reported by Cooper et al. [17] in 1951. Intraocular lymphoma develops commonly in individuals in their 50s and 60s, and the ratio of male to female patients is reported as 1.0:1.5 [16, 18]. In this series, the average age at onset of intraocular lymphoma was 63.4 years and there were more women (132 cases) than men (85 cases). In good agreement with a previous report [19], we found that blurred vision, reduced vision, and floater symptom were the common initial subjective symptoms that prompted patients to visit an ophthalmologist. The percentage of patients who had onset of intraocular lymphoma in both eyes was 66.7 % in this study, which is within the range (60–90 %) previously reported by Coupland et al. [20]. Although Grimm et al. [21] reported that behavioral and cognitive changes were the most common initial extra-ocular symptoms, followed by hemiparesis and headache, in the 221 patients with intraocular lymphoma with CNS involvement, we found that ataxia was the most common followed by dizziness

and headache. We also found that 132 of the 217 intraocular lymphoma patients (60.8 %) had CNS involvement, in good agreement with the high rates (60–90 %) reported previously [6, 9]. When patients are suspected as having intraocular lymphoma, CT and MRI should be performed to detect intracranial lesions. In addition, basic examinations such as detailed history taking and motor assessment of the upper and lower extremities are recommended. Our statistical analysis revealed that the interval between the onset of primary ocular lesions and subsequent onset of CNS lesions was 21.7 months, significantly longer than that between the onset of primary CNS lesion and subsequent onset of ocular lesions (12.5 months). This suggests that primary intraocular lymphoma tends to be relatively slow progressing, and correct diagnosis may be delayed if the case is diagnosed as an intraocular inflammatory disorder of unknown etiology. On the other hand, intracranial space-occupying lesions will be detected by CT and MRI in cases of primary CNS lymphoma, which will initiate brain biopsy or other suitable assessment method. In contrast, when an ophthalmologist has little experience with intraocular lymphoma, making a correct diagnosis on the basis of vitreous opacification only, for example, is extremely difficult. Although the features and extent of vitreous opacification were not investigated in this study, the characteristics of vitreous opacification associated with intraocular lymphoma include the presence of aggregation of large cells, strand formation, and aurora-like appearance (observation of vitreous opacity as if synchronizing with eye movement by binocular ophthalmoscope and/or scanning laser ophthalmoscope) confirmed by kinetic observation. Knowledge of these characteristics, together with an understanding of the common clinical findings of intraocular lymphoma, for example subretinal infiltrates (e.g. yellowish patchy lesions with multiple brown dots) and resistance to conventional anti-inflammatory treatment will help ophthalmologists to identify suspicious cases as intraocular lymphoma.

Vitrectomy was first performed for diagnosis of intraocular lymphoma by Klingele et al. [22] and Michels et al. [23] in 1975. Cytological examination of vitreous biopsy specimens has since come to be regarded as essential for definitive diagnosis of intraocular lymphoma, and is reported to achieve a very high positive rate [13, 24]. In this study, however, only 87 of 183 patients (47.5 %) were cytologically positive. The possible reasons for this low positive rate may include the effect of corticosteroids administered because of misdiagnosis of uveitis, cell damage by the vitreous cutter, or the effects of whole-brain irradiation performed before vitrectomy on patients with primary CNS lesions preceding the onset of ocular lesions. Another reason for the difficulty of diagnosis by cytology is that lymphoma cells degenerate easily and become necrotic rapidly. Therefore, it is important to transport and process the vitreous specimens promptly.

Cytokine analysis of the vitreous specimens is a supplementary diagnostic method and an intravitreal IL-10/IL-6 ratio greater than 1.0 is suggested as the diagnostic criterion of lymphoma by Whitcup et al. [6]. The sensitivity based on this criterion is reported to be 75 % [25], whereas that of detecting IgH gene rearrangements is 64 % [7]. In this study, the positive rates (sensitivities) for intravitreal IL-10/IL-6 ratios greater than 1.0 were 90.7 % (148/163 cases) and for IgH gene rearrangements 80.8 % (63/78 cases). Both are higher than previously reported rates, suggesting that these examinations are useful as supplementary diagnostic methods. However, among the 52 patients examined by all three tests (cytological examination, cytokine analysis, and molecular analysis), only 10 cases (19.2 %) tested positive for all three.

Our analysis showed that positive rates of cytological analysis and IgH gene rearrangements were different in patients with vitreous opacification and those without, whereas the positive rate for IL-10/IL-6 ratio greater than 1.0 was constantly high ($\geq$90 %) irrespective of the presence of vitreous opacification. A previous study suggests that subretinal aspiration biopsy can be useful for diagnosing intraocular lymphoma in patients with subretinal lesions when vitreous opacification is absent [26]. Alternatively, on the basis of its less invasive nature and high positive rate irrespective of vitreous opacification, cytokine analysis is useful for diagnosing intraocular lymphoma. Yet despite the fact that cytological analysis is considered to be a definitive diagnostic method, its results in this study had low positive rates (44.5 %), hence supplemental cytokine analysis and molecular analysis should be performed more frequently to confirm the diagnosis of intraocular lymphoma.

This study revealed the clinical features and diagnostic findings of intraocular lymphoma in Japan. There were few differences between our findings and the results of previous studies by an international group from North America, Europe, and Australia [17] and in the US [27] on the clinical features and diagnostic significance of intraocular fluid. As this study is the first large survey of intraocular lymphoma in Asia it may serve as a guide for intraocular lymphoma in Asian populations.

Early diagnosis enables early treatment, and this will lead to improvement of survival prognosis. Freeman et al. [13] reported the clinical features of 32 cases in 1987 (18 ocular and CNS, 7 ocular only, and 7 others). In their report, the 5-year survival rate was less than 30 %. In this study on the other hand, the 5-year survival rate improved to 61.1 %. Although the high percentage of cases presenting with primary intraocular lymphoma without CNS involvement may be an important factor accounting for the

high 5-year survival rate, we also hypothesize that earlier diagnosis (such as several monthly cranial MRI) and treatment of primary intraocular lymphoma may help prevent CNS involvement. On the other hand, compared with previous reports, the survival prognosis of intraocular lymphoma may be gradually improving because of the improvement in the accuracy of diagnosis and therapeutic strategies. In terms of treatment, intraocular lymphoma with preceding primary CNS lesions is led by a neurosurgical physician and/or a hematologist, and whole brain radiotherapy and systemic chemotherapy including high-dose methotrexate administration are considered good options. Moreover, patients with metastatic intraocular lymphoma are often on systemic chemotherapy after visiting a hematologist. However, there is no concrete consensus on the treatment of patients with primary intraocular lymphoma who have not yet developed lesions in other organs. Ocular irradiation [28], intravitreal methotrexate injection [29–31], and systemic chemotherapy based on high-dose methotrexate [32] have been attempted solely or in combination, but selection of the therapies is at the discretion of the ophthalmologists. We plan to analyze the treatments given and the prognosis of the large number of intraocular lymphoma patients examined in this study in order to develop a therapy that improves the survival prognosis of patients with intraocular lymphoma.

In conclusion, a retrospective review of 217 patients with intraocular lymphoma diagnosed in 25 institutions in Japan identified blurred vision and ataxia as the most common ocular and extra-ocular symptoms, and vitreous opacification as the most prevalent ocular finding. This series was characterized by a higher percentage of primary intraocular lymphoma (82.5 %), and higher 5-year survival rate (61.1 %). Among the diagnostic methods using vitreous biopsy, the IL-10:IL-6 ratio was the most reliable and sensitive index, followed by IgH gene rearrangement, with cytology the least sensitive. Cytokine analysis should be performed more frequently as a supplementary test to confirm a diagnosis of intraocular lymphoma.

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Appendix

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