A case of intraocular lymphoma with central nervous system involvement and high interleukin-10 levels in both vitreous humor and cerebrospinal fluids: successful treatment with a combination of intravitreal, intrathecal, and systemic therapy

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Abstract A 70-year-old man with diffuse large B cell lymphoma, who had been in complete remission without treatment, presented with a visual disorder in the right eye. Vitreous biopsy was performed, although the results were not typically suggestive of lymphoma. The concentration of interleukin-10 (IL-10) in the vitreous humor was markedly elevated, suggesting intraocular lymphoma (IOL). Weekly intravitreal injections of methotrexate (MTX) resulted in remission of the visual disorder. During this remission, 10 months after the last intravitreal MTX treatment, a cerebral tumor was observed in the corpus callosum and atypical lymphocytes were detected in the cerebrospinal fluid. The concentration of IL-10 in the CSF was markedly elevated and the IL-6 level was slightly elevated, suggesting central nervous system (CNS) involvement. The patient was treated with intrathecal MTX, systemic rituximab, high-dose cytarabine, and high-dose methotrexate. After this therapy, the cerebral tumor disappeared, atypical lymphocytes were undetectable in the CSF, and the CSF IL-10 level was significantly reduced. IL-10 and IL-6 concentrations in the vitreous humor and

CSF are important for diagnosis of IOL with CNS involvement and for monitoring the efficacy of therapy.

Keywords Intraocular lymphoma · Methotrexate · Interleukin-6 · Interleukin-10

Introduction

Intraocular lymphoma (IOL), first described in 1951, is infiltration of the vitreous humor and retina by lymphoma cells, secondary to tumor infiltration, retinitis, and vasculitis [1–3]. IOL is a subtype of primary central nervous system lymphoma (PCNSL), usually of the B cell type [4, 5]. In patients with IOL, disease was limited to the eye in 22 % and later involved the CNS in 56–85 % [4, 6]. For patients with IOL mortality is high, and the optimum therapy has yet to be determined. Intravitreal injection of methotrexate (vMTX) has been reported to be effective for IOL [7]. Systemic treatment with high-dose MTX plus Ara-C has been used for patients with IOL who had achieved remission of IOL and CNS lymphoma [8]. Interleukin-10 (IL-10) is a growth and differentiation factor for activated B cells, and is also an immunosuppressive cytokine that inhibits cell-mediated immunity via inhibition of Th1 cytokines [9]. IL-10 participates in the proliferation of IOL cells and in the protection of IOL from the immune system. Interleukin-6 (IL-6) levels are higher in the vitreous humor of patients with uveitis [10]. An increase in IL-10 levels in the vitreous humor, and an increase in the IL-10/IL-6 ratio to >1 has been reported in the vitreous humor of patients with IOL [6, 11]. In addition, elevated CSF IL-10 levels have been detected in PCNSL involving the vitreous humor [11]. We report a case of IOL with CNS involvement and high IL-10 levels, in both the

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vitreous humor and the CSF, which was successfully treated by use of a combination of MTX therapies.

Case report

A 70-year-old man presented with cervical, axillary, para-aortic, and inguinal lymph node swelling as determined by PET-CT on January 2007. Pathological examination of the cervical lymph node biopsy revealed diffuse large B cell lymphoma (DLBCL) (Fig. 1), and this specimen was positive for CD19 and CD20, and negative for CD3, CD5, and CD10 by flow cytometric analysis; chromosomal analysis showed normal karyotype. He was treated with rituximab in addition to the standard cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy regimen. After 8 courses of the R-CHOP regimen, a complete response (CR) was achieved by August 2007. He underwent no further treatment for 31 months after CR, but presented with a visual disorder and blurring

of vision in the right eye in March 2010. His corrected visual acuity was 0.5 in the right eye, and 1.0 in the left eye. Fundoscopic examination resulted in a diagnosis of uveitis in the right eye, and topical corticosteroid treatment had been administered in previous ophthalmology. However, his ocular symptoms did not improve over the next 3 months. The right eye showed severe white vitreous opacity, retina vasculitis, and a subretinal exudate on funduscopy (Fig. 2a). Therefore, a vitreous biopsy was performed, and the possibility of lymphoma was considered, but the biopsy sample was not typically suggestive of malignant lymphoma upon pathological examination. At the time of examination, the concentration of IL-10 in the vitreous humor was measured, and was found to be markedly elevated (817 pg/ml, normal <5 pg/ml), whereas the concentration of IL-6 was below the sensitivity of measurement (normal <4 pg/ml). These ocular symptoms and the increase in the IL-10/IL-6 ratio were suggestive of IOL. On the basis of these findings, the patient was treated by intravitreal injection of 400 µg MTX into the right eye

Fig. 1 Cervical lymph node biopsy: DLBCL. **a** H&E stain ×100, **b** H&E stain ×400

Fig. 2 The right eye showed signs of uveitis, severe white vitreous opacity, and subretinal exudate on funduscopy (**a** at the time of IOL diagnosis). These ocular findings disappeared, and macular degeneration and angiogenesis were seen on funduscopy (**b**, 6 months after the sixth intravitreal injection of 400 µg MTX, 8 doses of tMTX, and 4 courses of systemic R-HD-MTX/Ara-C therapy)

Fig. 3 A mass of 3–4 cm was seen in the corpus callosum on enhanced brain MRI at the time of diagnosis (**a** T1 axial view, **b** T1 sagittal view). The mass was not visible on a brain MRI taken after a combination of tMTX and systemic R-HD-MTX/Ara-C therapy (**c** T1 axial view)

once a week for 6 weeks. After the sixth vMTX, the patient's corrected visual acuity recovered to 1.0, and the ocular findings had improved.

In January 2011, 10 months after the last vMTX treatment, he presented for the first time with CNS symptoms of sluggishness and dizziness. Therefore, brain MRI was performed and revealed a 3–4 cm mass in the corpus callosum (Fig. 3a, b). We performed a lumbar puncture, and found 750 atypical lymphocytes with mononuclei positive for anti-CD20 antibody in the CSF (Fig. 4). These lymphocytes also tested positive for an immunoglobulin heavy chain (IgH) gene rearrangement, as determined by polymerase chain reaction (PCR), and the concentration of IL-10 in the CSF was markedly elevated to 7920 pg/ml. The concentration of IL-6 in the CSF was slightly elevated at 46.2 pg/ml, and the IL-10/IL-6 ratio was 171.4 (Table 1). An increase in the CFS IL-10/IL-6 ratio to >1 has been reported in patients with PCNSL [11, 12]. However, the level of the soluble interleukin-2 receptor had increased to 682 U/ml at the time of appearance of the ocular symptoms but had, since then, been maintained within the normal range until the appearance of CNS symptoms.

Although it was difficult to perform a brain biopsy, these findings suggested that the CNS, including the brain and spinal cord, were involved in the IOL. On the basis of these findings, the patient was diagnosed as having CNS involvement in IOL, and a recurrence of DLBCL after the first CR for 41 months. He was treated with systemic 375 mg/m² rituximab on day 1, 2.0 g/m² MTX with leucovorin rescue on day 2, and 2.0 g/m² Ara-C twice a day on days 3 and 4 (R-HD-MTX/Ara-C regimen), the dose of MTX was reduced because of advanced age. In addition, he was treated with intrathecal MTX (15 mg/body) plus Ara-C (40 mg/body) plus dexamethasone (20 mg/body) (tMTX regimen) once every 2 weeks, for a total of 8 treatments.

Fig. 4 Atypical lymphocytes with mononuclei were found in the cerebral spinal fluid (CSF) by lumbar puncture (May-Giemsa stain)

After 4 courses of the R-HD-MTX/Ara-C and tMTX regimens, the mass in the corpus callosum was not visible on MRI (Fig. 3c). Furthermore, the level of IL-10 in the CSF after the combination of these therapies was dramatically reduced to 17 pg/ml, compared with 7920 pg/ml before therapies (Table 1). The number of atypical lymphocytes in the CSF also markedly decreased to 7 cells, after these regimens. The patient's ocular findings were also significantly improved, and his right eye visual acuity was restored (Fig. 2b).

Discussion

IOL has two distinct forms:

1. arising in the CNS and/or the retina (primary IOL); and
2. arising outside the CNS with intraocular metastasis (metastatic IOL) [13].

Table 1 Atypical lymphocyte counts with mononuclei, and IL-10 and IL-6 levels in the CSF before and after a combination of tMTX and systemic R-HD-MTX/Ara-C therapy

	Before therapy	After therapy
CSF cell count	750	7
CSF IL-10 (pg/ml)	7920	17
CSF IL-6 (pg/ml)	46.2	4.3
IL-10/IL-6 ratio	171.4	3.9

IL-10, normal <5 pg/ml; IL-6, normal <4 pg/ml

This case was classified as a metastatic IOL, because he had a history of systemic chemotherapy for DLBCL in the past. The absence of lymphoma cells in the vitreous biopsy could have been because of the cytolytic effect of the topical corticosteroid treatment for presumed uveitis, which would reduce the likelihood of positive cytological diagnosis of malignant lymphoma by vitreous biopsy [4]. A markedly elevated IL-10/IL-6 ratio in the vitreous humor aids in diagnosis of IOL, when it is not possible to diagnose by retinal biopsy, as in this case. Vitreous samples from 22 patients with clinically suspected IOL and control patients with acute retinal necrosis or cytomegalovirus retinitis were examined for these cytokines. In patients with IOL, IL-10 concentrations were significantly higher than those of IL-6, whereas in control patients, the IL-6 concentrations were significantly higher than those of IL-10 [14]. In addition, when brain biopsy is locally difficult, as in this case, a combination of measurement of these cytokines and a PCR assay to detect IgH gene rearrangement, in the CSF, is extremely useful for diagnosing CNS involvement. In patients with IOL and PCNSL, levels of IL-10 exceeded those of IL-6 in 6 of 11 CSF samples with lymphoma cells, compared with 7 of 53 samples without lymphoma cells [11]. In this case, the significant increase of IL-10 concentration and involvement with DLBCL cells in the CSF was reduced, with a decline of these cell counts, by treatment with tMTX and HD-MTX/Ara-C regimens (Table 1). The major difficulty in using chemotherapy to treat IOL with CNS involvement is the presence of the blood–ocular and blood–brain barriers. The ability of MTX and Ara-C to penetrate these barriers has led to their use in chemotherapy regimens [15].

Although systemic chemotherapy alone can result in a high response of patients with IOL, the incidence of relapse is a high. In one study [16], to improve survival, 21 IOL patients with CNS involvement were treated with combined chemotherapy and radiation. Seventy-nine patients aged 18–75 years, with DLBCL exclusively localized in the CNS, received 4 courses of either 3.5 g/m² MTX on day 1 alone ($n = 40$) or 3.5 g/m² MTX on day 1 plus 2.0 g/m² Ara-C twice a day on days 2–3 ($n = 39$). Both regimens were administered every 3 weeks and were

followed by whole brain irradiation with 36–40 Gy. The CR rate was 18 and 46 % and the overall response rate was 40 and 69 %, respectively. In this study, very high efficacy was observed when Ara-C was used with HD-MTX for systemic chemotherapy and radiation.

On the basis of these reports, the International Primary Central Nervous System Lymphoma Collaborative Group (IPCG) recently issued treatment guidelines for IOL, as follows

1. IOL without CNS or systemic involvement: (a) If only one eye is involved, use local therapy. Whether local intravitreal MTX and rituximab or 30–35 Gy of external beam radiotherapy should be used is still a matter of debate. (b) If both eyes are involved, add intravitreal chemotherapeutic agents to systemic therapy.
2. IOL with CNS involvement: (a) Treat with HD-MTX-based chemotherapy with rituximab and local therapy. (b) Whole-brain radiotherapy with ocular radiotherapy should be considered in those who have failed systemic chemotherapy and aggressive therapy, for example autologous stem cell transplantation (ASCT) [17].

In this case, because IOL involved one eye, without CNS involvement, at the time of diagnosis, it was treated with vMTX alone, and we continued examining the patient's CNS findings for 10 months from the onset of the last treatment of vMTX. Subsequent CNS involvement complicated this patient's treatment, because systemic therapy was necessary. To the best of our knowledge for this case, even if there was no CNS findings, vMTX and systemic MTX regimen should have been administered sequentially. We suggest that once diagnosis of IOL is established, neurological staging, including brain MRI and lumbar puncture, should be performed. A survival benefit is more likely when treatment is initiated early with a combination of vMTX, tMTX, and systemic R-HD-MTX/Ara-C, with or without radiation therapy and/or ASCT. However, in the case of advanced age, whole-brain radiotherapy and ASCT must be evaluated as they could be accompanied by the risks of leukoencephalopathy and systemic complications, respectively.

Conflict of interest No author has any conflict of interest.

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