지속적인 완전 관해 후 유리체염만으로 재발이 의심되는 자궁의 광범위B형대세포림프종

Presumed Ocular Relapse of Diffuse Large B Cell Uterine Lymphoma Presenting Only as Vitritis after Continuous and Complete Remission

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Purpose: To report an ocular relapse of diffuse large B cell uterine lymphoma.

Case summary: A 51-year-old woman with diffuse large B cell uterine lymphoma reached and maintained complete remission for four consecutive years at six re-staging evaluations after six cycles of cyclophosphamide, hydroxyl-daunorubicin, oncovin, and prednisone chemotherapy. Late ocular relapse of diffuse large B cell lymphoma may simply present as cells in the vitreous cavity without any systemic involvement. Diagnostic vitrectomy was performed, and the cytopathologic exam showed monoclonal B cell origin lymphoma. The patient was given a repeat course of intravitreal methotrexate injections and six cycles of high-dose methotrexate and Ara-C intravenously. Despite the chemotherapy, brain involvement was detected 26 months after the diagnosis. However, the patient remains alive after 48 months.

Conclusions: In selected patients with intraocular lymphoma, having a high degree of clinical suspicion is the most important factor required to make the diagnosis; diagnostic vitrectomy is useful for both diagnostic and therapeutic purposes.

Keywords: Diagnostic vitrectomy; Diffuse large B cell lymphoma; Intraocular lymphoma; Intravitreal methotrexate injection; Uterine lymphoma

Introduction

Primary uterine lymphoma is a rare cancer with an unknown etiology and pathogenesis, although previous studies and clinical experiences show a possible association between chronic inflammation and lymphomas [1]. According to a recent publication on early stage, low-grade lymphoma, diffuse large B cell lymphoma is the most common type. The

cyclophosphamide, hydroxyl-daunorubicin, oncovin, and prednisone chemotherapy regimen (R-CHOP) has proven to be effective, having a cure rate of 70-80% [2,3]. However, patients treated for diffuse large B cell lymphoma are at continued risk of late relapse [4]. Herein, we report an unusual case of a relapsed intraocular lymphoma patient who had previously achieved complete remission. Diagnosing the recurrence was challenging because it is likely to first suspect

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Figure 1. Histologic images of uterus and vitreous. (A) At the time of diagnosis of primary uterine lymphoma, histologic findings of the uterus and its adnexa showed a malignant lymphoproliferative lesion spread over the mesosalpinx and the left ovary. Hematoxylin and eosin staining, $\times 100$ original magnification (B), $\times 400$ original magnification (C), immunophenotypic characterization of the diffuse large B cell lymphoma revealed this to be CD20 positive (C). (D) At the time of the relapsed intraocular lymphoma diagnosis, diagnostic vitrectomy revealed atypical lymphocytes that were CD20 positive, hematoxylin and eosin staining, $\times 400$ original magnification.

a second primary cancer or a benign side effect of an earlier treatment rather than a relapse due to its rarity. Additionally, lymphoma can masquerade as different types of uveitic entities. The only presenting sign in this case was vitritis in both eyes without systemic involvement.

Case Report

A 51-year-old woman presented with gradual visual disturbance associated with vitreous floaters over the past six months. One month prior to the event, she had noticed an abrupt increase of floaters in both eyes. Her visual acuity measured 10/20 with correction in the right eye and 12/20

with correction in the left at initial presentation. Intraocular pressure and anterior segment examination were normal in both eyes. Two weeks prior to the visit to our clinic, she had been treated with oral prednisolone (40 mg/day) for two weeks for a diagnosis of severe intermediate uveitis. However, there was no symptomatic improvement, and laboratory results, including complete blood count, blood chemistry for noninfectious uveitis and titers for infectious agents, were negative for the source of her disease.

After reviewing her past medical history, we learned that she had visited a hospital for a lower abdominal mass and underwent a total hysterectomy with bilateral adnexectomy four years ago. Histologic findings of the uterus and its adnexa showed a malignant lymphoproliferative lesion that had

Figure 2. Preoperative and postoperative images. (A) Ophthalmologic examination showed vitreous cells and opacity in the vitreous body, which was worse in the right eye. (B) Fluorescein angiography revealed diffuse capillary leakage. (C) Optical coherent tomography did not suggest retinal or choroidal involvement. (D) Eighteen months after the diagnosis, the patient's visual symptoms had improved and a fundus exam showed resolution of vitreous cells and no recurrence in the right eye, which received a diagnostic vitrectomy and adjuvant intravitreal methotrexate (MTX) injections. The left eye, which was treated only with intravitreal MTX injections, also showed an almost complete resolution of the vitreous cells.

spread to the mesosalpinx and the left ovary. The immunophenotypic characterization of diffuse large B cell lymphoma demonstrated CD20 positivity (Fig. 1A-C). Physical examination and laboratory results, including lactic dehydrogenase, were unremarkable. Complete systemic staging, including positron emission tomography/computed tomography (PET/CT) scan, lumbar puncture, and bone marrow biopsy, were all negative. The patient was diagnosed with stage IE diffuse large B cell lymphoma of the uterus and the left ovary. The international prognostic index was 0. The patient was treated with R-CHOP for six cycles and achieved complete remission. She maintained a state of remission for

Figure 3. Corneal complications during intravitreal methotrexate (MTX) injections. (A) After completing the induction phase of intravitreal MTX injections, the patient had developed a corneal epithelial defect. (B) Marginal keratitis also had developed.

Figure 4. Brain MRI images 26 months after initial diagnosis. (A, B) Despite intravitreal MTX injection followed by systemic chemoprophylaxis, brain MRI revealed multiple focal enhancing nodules with surrounding edema in the bilateral fronto-parietal lobes (arrows). MRI = magnetic resonance imaging; MTX = methotrexate.

four consecutive years at six restaging evaluations.

Ophthalmologic examination revealed vitreous cells (vitritis) and opacity in the vitreous body, which was particularly worse in the right eye (Fig. 2A). Fluorescein angiography showed diffuse capillary leakage (Fig. 2B); however, optical coherent tomography did not indicate retinal or choroidal involvement (Fig. 2C). From a clinical point of view, lymphoma cells in the vitreous may have been an indicator of the initial phase of central nervous system (CNS) involvement. We were suspicious of a CNS relapse, but magnetic resonance imaging (MRI) of the orbit and the brain demonstrated no remarkable findings; lumbar puncture with cytologic examination of the cerebrospinal fluid showed no neoplastic cells. Thus, the patient underwent diagnostic vitrectomy in her right eye.

For an accurate diagnosis, it was necessary to obtain as undiluted a specimen as possible without any complications, such as suprachoroidal hemorrhage. We connected the three-way system to the vitrectomy cutter and attached the syringe to one side so that it did not enter the cassette. Undiluted vitreous (1.5 mL) was first obtained using a vitrectomy cut-

ter with the infusion off for cytology, cytokine analysis and gene rearrangement. An initial diluted specimen (4.0 mL) was also obtained with the infusion on. These fluids were immediately transported to the awaiting cytology laboratory for rapid processing and appropriate handling. Finally, a specimen of the remaining vitreous wash was obtained through the cassette and sent for analysis after surgery.

Cytologic examination of the vitreous showed large atypical lymphoid cells with large and irregular nuclei and prominent nucleoli, which were immunoreactive for CD20 (Fig. 1D). Immunophenotyping results obtained from flow cytometry were also suggestive of monoclonal B cell lymphoma. The supernatant of the vitreous specimen was used for the cytokine analyses. The interleukin 10 (IL-10) to IL-6 ratio was 98.5, which was greater than 1.0 and therefore highly suggestive of lymphoma. Monoclonality was also confirmed in these cells using polymerase chain reaction (PCR). However, bone marrow biopsy showed a normocellular appearance without lymphoma invasion.

All the results were consistent with diffuse, large B cell intraocular lymphoma. During the following months, the patient was given intravitreal methotrexate (MTX) injections of 400 µg/0.1 mL in both eyes. She received a total of 16 intraocular injections, 8 for each eye, in accordance with the twice-a-week Frenkel protocol during the first month of the induction phase. However, after completing the induction phase, she developed corneal epitheliopathy (Fig. 3), which is a major complication of intravitreal MTX injections. The scheduled injections had to be stopped, and treatment of the damaged corneal epithelium was carried out using autoserum and preservative-free artificial tear eye drops. Complete healing of the epithelium was observed. One month later, we restarted the consolidation regimen of one injection per week for a month. While she was receiving the ophthalmologic treatments, a restaging workup was done that included a PET/CT scan, which revealed negative results. Involvement in the lymph nodes or other extranodal sites, such as the CNS, was not seen. During the ocular consolidation, the patient also received intravenous, high-dose MTX and Ara-C to prevent both systemic and CNS recurrence. Twenty-four months after the diagnosis, her best-corrected visual acuity had improved to 20/20 in the right eye and 16/20 in the left. Her visual symptoms had also improved, and a fundus exam showed resolution of the vitreous cells with no sign of recurrence in the right eye, which had undergone a prior vitrec-

tomy. The left eye, which was treated only with intraocular injections, also showed near complete resolution of the vitreous cells (Fig. 2D). Despite six cycles of chemotherapy, brain involvement with malignant lymphoma was detected 26 months after the initial diagnosis (Fig. 4). Forty months after her diagnosis, the patient is currently alive after 10 cycles of chemotherapy, with a visual acuity of 20/20 in the right eye and 16/20 in her left.

Discussion

Intraocular lymphoma is a rare disease, which accounts for 1% of non-Hodgkin's lymphoma and less than 1% of all intraocular tumors [5]. These lymphomas arise in different parts of the eye. According to their locations, they can be divided into further sub-classifications, such as retinal lymphoma (retinal, vitreoretinal, vitreal) and uveal lymphoma (choroidal, ciliary, iridal) [6]. Intraocular lymphoma usually refers to those types that predominantly involve the retina and vitreous. However, in systemic metastatic lymphomas, the uvea is the most common site of involvement. Systemic metastatic lymphoma of the retina and vitreous without uveal or conjunctival involvement is exceptionally rare [7].

In our case, the initial invasion of systemic lymphoma into the vitreous, which was the solely involved site, rendered the diagnosis more difficult. Interestingly, other retinal specialists were misled into misdiagnosing the condition as non-infectious intermediate uveitis; they treated the patient with steroids for two weeks. This treatment provided an additional challenge to the actual diagnosis because prior treatment with steroids may lower the diagnostic yield and increase the chances of a negative result upon vitrectomy biopsy [8].

Successful confirmatory biopsy by fine-needle aspiration or vitrectomy is a demanding procedure that requires significant skill by the ophthalmologist and also the cytopathologist [9]. Cytopathologists employ other supplementary methods, such as flow cytometry, immunohistochemistry, cytokine analyses, and molecular analysis, due to the limited amount of malignant cells that may be present in the specimen. These diagnostic tests are not definitively diagnostic of metastatic lymphoma and also cannot differentiate metastatic lymphoma from primary intraocular lymphoma. However, they can be useful adjunctive tests in assuring a clinical suspicion of malignant lymphocytes in the eye [6,10].

Intravitreal MTX has been used to treat both isolated and recurrent ocular lymphoma. It avoids systemic toxicity and provides a longer duration of therapeutic intraocular drug levels. Early systemic treatment for intraocular lymphoma may delay the onset of CNS disease, prolonging patient survival [11]. However, it remains unclear whether ocular therapy has any impact on overall survival because approximately 80% of patients with primary intraocular lymphoma subsequently develop lymphoma of the brain, spinal cord or meninges.

Because these are extremely rare cancers, there is little consensus regarding the management and treatment of the disease due to difficulty in finding enough patients to participate in clinical studies. A recent report suggested that an earlier diagnosis and treatment of primary intraocular lymphoma could help prevent CNS involvement. Furthermore, ocular tumor control might become more important in the overall survival rates with improvements in the treatment of CNS lymphoma [12]. In our case, we administered intravitreal injections of MTX to treat intraocular lymphoma followed by systemic chemotherapy. Despite the patient's relapse in the brain 26 months after the initial diagnosis, early treatment likely aided in her survival until now, which has been a period of over 48 months.

There have been several reports of metastatic intraocular lymphoma. These secondary intraocular lymphomas represented ocular involvement in the setting of systemic lymphoma [13,14]. However, to our knowledge, this is the first report of a patient with diffuse large B cell uterine lymphoma treated with R-CHOP chemotherapy who experienced ocular relapse that presented with isolated visual complaints merely due to vitreous malignant cells without retinal infiltration following complete remission.

There is a possibility that the patient may have newly developed primary intraocular lymphoma. To determine whether the CNS lymphoma was clonally related to the first lymphoma, rearrangement of the immunoglobulin heavy chain genes of each lymphoma was investigated using a PCR-based method [15]. The limited number of malignant cells in the vitreous prevented us from performing clonal analysis of metastatic vitreal lymphoma cells to rule out this possibility. However, a previous study showed that relapses usually occur within the first five years [15] and that most late relapses in patients with diffuse large cell lymphoma have been found to be of B cell origin. Thus, in our case, we

assumed that the most likely diagnosis of the relapse would be diffuse large B cell lymphoma.

In this report, we emphasized that clinical suspicion is the most important component in confirming the diagnosis of ocular lymphoma. Intraocular lymphoma should be considered when uveitis develops, even if the patient has an early stage of low-grade lymphoma or has achieved complete remission.

Conflicts of interest

The authors declare that they have no competing interests.

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