Bilateral Central Retinal Vein Occlusion in a Patient with Mantle Cell Lymphoma

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Abstract

Background: A Mantle Cell Lymphoma (MCL) is an aggressive B cell lymphoma and accounts for approximately 6% of all Non-Hodgkin’s lymphomas. A MCL has a poor prognosis with a median survival of about two to five years. We present our findings in a case of bilateral Central Retinal Vein Occlusion (CRVO) that developed in a patient with MCL.

Case Presentation: A 70-year-old woman was diagnosed with primary tonsil MCL in March 2009 and progressed to complete remission after eight cycles of R-CHOP (Rituximab, Cyclophosphamide Hydroxydaunorubicin, Vincristine and Prednisone) chemotherapy. In July 2010, she had a recurrence of the lymphoma in the gastric mucous membrane, tonsils and pharynx but no additional treatment was given because she had no symptoms and the size of the tumors was small. In January 2014, metastases were detected in the cervical, supravacular and inguinal lymph nodes and the size of the tumors in the gastric mucous membrane, tonsils and pharynx were larger. However, the Central Nervous System (CNS) was not invaded as determined by fluorodeoxyglucose positron emission tomography/computer tomography. Thus, a salvage therapy was instituted in April 2014. She had been diagnosed with Sjogren’s syndrome in 2008 when the antiphospholipid antibody and the autoantibody were negative on blood tests. The medical condition was stabilized with an oral intake of 10mg of pilocarpine.

In March 2014, the vision in her right eye decreased, and two weeks later at the first visit to our hospital, the decimal Best-Corrected Visual Acuity (BCVA) was 0.01 OD and 1.0 OS. Slit-lamp biomicroscopy showed that the anterior segments and the anterior chamber angles were normal. The Intraocular Pressures (IOPs) were normal in both eyes. Fundus examination showed retinal hemorrhages and dilatation and tortuosity of the veins in all quadrants and cotton wool spots and macula edema in the right eye. A few widely-scattered, flame-shaped retinal hemorrhages and mild vascular tortuosity were present in the left eye. Optical Coherence Tomography (OCT) showed cystoid macula edema in the right eye (Figure 1). Fluorescein angiography demonstrated a marked delay in the arteriovenous transit time, masking by the retinal hemorrhages, and late staining along the large retinal veins. A few non-perfused areas were also present in the right eye and a slight increase in retinal circulation time in the left eye (Figure 2).

She was diagnosed with a right CRVO with macula edema and an impending CRVO in the left eye. An intravitreal ranibizumab injection was done on the right eye. Spinal puncture was performed by her primary physician to determine whether the CNS was involved but no symptoms and the size of the tumors was small. The anterior segments and the anterior chamber angles were normal. The Intraocular Pressures (IOPs) were normal in both eyes. Fundus examination showed retinal hemorrhages and dilatation and tortuosity of the veins in all quadrants and cotton wool spots and macula edema in the right eye. A few widely-scattered, flame-shaped retinal hemorrhages and mild vascular tortuosity were present in the left eye. Optical Coherence Tomography (OCT) showed cystoid macula edema in the right eye (Figure 1). Fluorescein angiography demonstrated a marked delay in the arteriovenous transit time, masking by the retinal hemorrhages, and late staining along the large retinal veins. A few non-perfused areas were also present in the right eye and a slight increase in retinal circulation time in the left eye (Figure 2).

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Two weeks later, her BCV A decreased to 0.02 OD and 0.03 OS. Ophthalmoscopy showed that there was neovascularization on the optic disc of the right eye, and retinal hemorrhages and severe dilation and tortuosity of the veins in all quadrants of the left eye. In addition, macula edema was detected in the left eye, and OCT showed cystoid macula edema in both eyes (Figure 3).

We began Panretinal Photocoagulation (PRP) on the right eye to prevent Neovascular Glaucoma (NVG), and ranibizumab was injected intravitreally in the left eye on the same day. Fluorescein angiography showed delayed venous filling consistent with a CRVO with several non-perfused areas in the left eye (Figure 4). Magnetic resonance imaging was performed and no thickening of the optic nerve and no enhancement of the optic-nerve-sheath complex was detected in a post-contrast examination.

Although there were only a small number of non-perfused areas in the fluorescein angiograms, we began PRP on the left eye to prevent the development of NVG. Although the causal relationship was weak between CRVO and MCL, we recommended further treatment for MCL to physicians because bilateral CRVO may be a clinical sign of a relapsing malignant ocular lymphoma. A second cycle of chemotherapy with bendamustine was performed by her primary physician. However, further chemotherapy was not done because of episodes of malaise and anorexia after the second cycle.

Later, we performed five intravitreal injections of aflibercept for the macula edema. The macula edema was well managed and NVG was prevented for the next 16 months. The decimal BCV A at 16 months after the onset was 0.03 OD and 0.02 OS and did not improve.

**Discussion**

We report our findings in a rare case of MCL that developed CRVOs bilaterally. The ocular involvements in patients with NHL occurs most commonly in its primary form which is considered to be a subtype of primary CNS lymphomas [7,8]. However, an intraocular lymphoma secondary to systemic lymphoma is not common and is usually limited to the uveal tract [5,9]. There are several reports of the optic nerve involvement in cases of systemic NHL [10-12]. Several cases of infiltrative optic neuropathy have also been reported which may be the first manifestation of a recurrence of the NHL [11,13].

It is difficult to determine the exact route of the metastatic spread of a systemic NHL to the optic nerve because there are several possibilities, e.g., a direct invasion by the tumor cells, hematogenous dissemination, dissemination through the CSF, and perineural spread to the optic nerve [14-16].

Several mechanisms are associated with the retinal vein occlusions in systemic NHL patients. There have been several reports of vascular occlusions secondary to a systemic NHL [7,17-19]. In one study, it was suggested that the vaso-occlusion was associated with the perivascular infiltration of lymphocytes through the laminarcribosa sclerae which...
led to the vaso-occlusion [7]. It is also believed that vein occlusions are associated with compression of the vascular wall by the lymphomatous optic nerve infiltration in these studies. The findings in other reports suggested that the vascular occlusions were associated with septic emboli and with paraneoplastic hypercoagulability [17,20,21].

In our case, there was no evidence of septic emboli and of hypercoagulability. In addition, there were no positive images showing a thickening of the optic nerve with enhancement of the optic nerve sheath complex, and no signs of metastasis to the CNS. Additionally, no lymphocytes were found in the CSF. In earlier cases, most patients who had the optic nerve involvement with systemic diseases had positive neuroimaging with enhancement of the optic nerve or positivity for malignant cells in the CSF [10-12,16].

Although it is difficult to determine the etiology of the vaso-occlusions in our case, there is the possibility that the optic nerve infiltration could be associated with the vaso-occlusions. In our case, the visual acuity did not recover in spite of good management of the macula edema. In a previous case of a patient with NHL who developed central artery and retinal vein occlusions, it was suggested that these occlusions were due to optic nerve infiltration that led to bilateral posterior ischemic optic neuropathy according to postmortem examinations [17]. There is a possibility of posterior ischemic optic neuropathy which may have influenced the visual acuity in our case. Another possibility of poor visual acuities is the possibility of co-morbidity central retinal artery occlusion because OCT findings showed significant intraretinal edema and homogenious band-like thickening.

After the on-label use of intravitreal aflibercept injection was permitted, intravitreal aflibercept injection becomes a first choice of the medical treatment for diabetic macular edema as well as RVO in our hospital [22]. Thus, we have switched from ranibizumab to aflibercept for the treatment of CRVO in this case.

From our experiences, in some cases it is difficult to control the IOP by performing PRP after the development of NVG. Thus, once we catch any signs of non-perfused areas, we start to perform PRP for preventing the development of NVG. For example, in case of management of diabetic retinopathy, we usually perform retinal photocoagulation for non-perfused areas in pre-proliferative diabetic retinopathy in Japan [23]. Thus retinal photocoagulation for non-perfused areas is a standard therapy for diabetic retinopathy and RVO in Japan.

Conclusion

In conclusion, we report an extremely rare case of a patient with MCL who developed bilateral CRVO. Even when the causal relationship is weak between CRVO and MCL, ophthalmologists should recommend further therapies for MCL to physicians because a CRVO may be a clinical sign of a relapsing malignant ocular lymphoma.

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