Original Study

Vitreoretinal Lymphoma: Changing Trends in Diagnosis and Local Treatment Modalities at a Single Institution

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Abstract

In this retrospective study on vitreoretinal lymphoma, there was significant change in diagnosis and treatment trends over 17 years at a single institution. Fine needle aspiration biopsy had replaced vitrectomy to collect vitreous sample and external beam radiotherapy in combination with systemic chemotherapy was replaced by intravitreal methotrexate and rituximab, which regressed vitreoretinal lymphoma (VRL) with no relapses or major ocular complications.

Introduction: The purpose of this study was to report the changing trends in treatment (external beam radiotherapy [EBRT] and intravitreal chemotherapy) of VRL and treatment outcomes at a single institution. **Materials and Methods:** A retrospective chart review of vitreous biopsy proven patients was performed. The data analysis included demographics, systemic lymphoma status, ocular symptoms, clinical and immunocytological findings, treatment methods, and response (intravitreal methotrexate 300 μg/0.05 mL, 1000 μg/0.1 mL of rituximab and EBRT 36-45 Gy) and ocular and systemic lymphoma outcomes at last follow-up. **Results:** Twelve eyes of 8 patients had intraocular B-cell lymphoma (median age, 61 years; range, 50-83). Central nervous system non-Hodgkin's lymphoma (CNS-NHL) was present in 7 of 8 patients. Most common ocular symptoms were diminution of vision in 4 and floaters in 3 patients. Iritis and uveitis were fournd in 6 eyes and vitritis in 11 eyes. Retinal infiltrates were present in 8 eyes. Immunocytology revealed elevated levels of interleukin (IL)-10 (12,783.5 pg/mL), IL-6 (26.7 pg/mL), and IgH gene rearrangement. Three patients were treated with EBRT, 6 eyes with intravitreal methotrexate (median, 9.5; range, 2-15), and 2 eyes with intravitreal rituximab injections (median, 4; range, 2-6). Two patients developed marked keratitis because of methotrexate toxicity. At median follow-up of 33.5 months (range, 4-96), VRL had resolved in 7 eyes and persistent in 5 eyes. One patient died because of advanced CNS-NHL. **Conclusion:** Intravitreal chemotherapy provided good control rates for VRL patients in our limited series. Patients with associated CNS-NHL had poorer outcomes.

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Introduction

Primary intraocular lymphoma (PIOL)/primary vitreoretinal lymphoma (PVRL) is very rare and it occurs frequently in association with central nervous system non-Hodgkin's lymphoma (CNS-NHL).[1-3] Vitreoretinal lymphoma (VRL) is usually of large B-cell lymphoma, but rarely T-cell lymphomas were also described.[4,5] PIOL involves vitreous, retina, subretinal space, and rarely optic nerve, whereas secondary intraocular lymphoma (IOL) represents metastasis to the uvea which is considered as low-grade, extranodal, marginal zone, B-cell type.[6-9] Diagnosis can be made by vitreous aspiration/biopsy cytology. Newer methods such as immunohistochemestry (CD3, CD19, CD20, CD22, and κ or λ chain restriction) and molecular markers (interleukin [IL]-6, IL-10, IgH, and T cell receptor gene rearrangement) were found to be very helpful in making a definite diagnosis of lymphoma.[7-13] There are various mo-

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Table 1 Demographic, Treatment Modalities, and Final Outcomes in Patients With Vitreoretinal Lymphoma

Patient Number	Age (Years)	Sex	Laterality	Ocular Symptoms	Previous Local Treatment	Current Local Treatment	VRL Status	Systemic Status
1	53	F	Bilateral	Blurry VA	Topical steroids	Intravitreal methotrexate	Persistent	Alive, persistent
2	61	M	Bilateral	Blurry VA with floaters		Intravitreal methotrexate, rituximab	Resolved	Alive, remission
3	57	M	Unilateral	Blurry VA	Topical steroids	EBRT	Resolved	Alive, remission
4	50	F	Unilateral	Floaters		Topical steroids and systemic CTx	Resolved	Alive, remission
5	83	F	Unilateral	Blurry VA		EBRT	Persistent	Alive, remission
6	61	M	Unilateral	Blurry VA		EBRT	Resolved	Alive, remission
7	71	F	Bilateral	Floaters	Topical steroids and vitrectomy	Topical steroids	Resolved	Alive, remission
8	80	M	Bilateral	Blurry VA with floaters	Topical steroids	Intravitreal methotrexate	Persistent	Dead, 2° to advanced disease

Abbreviations: CTx = chemotherapy; EBRT = external beam radiotherapy; F = female; M = male; VA = visual acuity; VRL = vitreoretinal lymphoma.

dalities in the treatment of VRL. Ocular external beam radiotherapy was effective in controlling the local disease, but central nervous system (CNS) parenchymal relapse, keratoconjunctivitis sicca, rubeotic glaucoma, cataract, vitreous hemorrhage, vascular retinopathy, optic atrophy, and radiation retinopathy as side effects has limited its use.[14-16] Topical and systemic corticosteroids were known to cause resistance of vitreous cells to treatment leading to resistance of the disease to them and thereby leading to progression. Localized chemotherapy using intravitreal methotrexate and rituximab was found to be well tolerated and effective in the treatment of VRL with fewer local side effects.[16-25] In our retrospective study, few patients were treated with external beam radiotherapy (EBRT) before intravitreal chemotherapy was available. Later on we switched the treatment to intravitreal chemotherapy. In our study, we report the clinical features, advanced methods in diagnosis and treatment, response of VRL to various modalities of treatment, and ocular and systemic outcomes.

Materials and Methods

A retrospective chart review of electronic medical records of patients presenting to the retina clinic with nonresponsive uveitis and vitritis between January 1995 to February 2012 (17 years) was performed. Only patients with vitreous biopsy proven lymphoma were included in analysis. There were many patients in the data system that were treated for suspected VRL but were not included in this study because of lack of biopsy results. The data recorded for analysis included demographic, systemic lymphoma status and treatment, ocular symptoms, clinical findings, optical coherence tomography (OCT), fluorescein angiography (FA), and immunocytological findings (vitrectomy specimens in 2 patients and vitreous aspiration biopsy in 6 patients), treatment methods (intravitreal methotrexate [300 μg/0.05 mL biweekly for 1 month, weekly for 1 month and monthly maintenance injections], 1000 μg rituximab in 0.1 mL once a month until corneal epitheliopathy stabilized and then switched back to methotrexate injections and EBRT [3600-4500 cGy]) and response to treatment. Ocular and systemic lymphoma outcomes at the last follow-up visits were also included. Statistical analysis was performed using SPSS version 17.0.

Results

Twelve eyes of 8 patients were included in the study of 17 years duration. All 8 patients were Caucasians, of which 4 were female and the other 4 were male (50%). The median age of patients was 61 years (range, 50-83) (Table 1). CNS-NHL was present in 7 of the 8 patients (87.5%). Systemic lymphoma was treated with chemotherapy in 4 patients (50%), EBRT in 2 (25%), and combined chemoradiation therapy in another 2 patients (25%). Before presentation to our center, 50% of patients were treated with topical steroids and the other 50% did not receive any treatment for eye disease. The most common ocular symptoms were diminution of vision in 5 (62.5%) patients, floaters in 4 (50%), and combined in 2 patients (25%). Four patients had bilateral disease at presentation (50%) and the other 4 had unilateral involvement (50%). Visual acuity was better than 20/40 in 5 eyes (41.7%), 20/50-20/100 in 2 eyes (16.6%), and worse than 20/200 in 5 eyes at presentation (41.7%). The median intraocular pressure (IOP) was 15 mm Hg (range, 8-38). Mild to moderate cataract was present in 11 eyes (91.7%). Iritis and uveitis were found in 6 eyes (50%) and vitritis in 11 eyes (91.7%). Retinal infiltrates were present in 8 eyes (66.7%) (Figure 1A). Drusen-like lesions in the macula were seen in 6 eyes (50%), and retinal pigment epithelial (RPE) changes (hyperplasia) were present in 5 eyes (41.7%) (Figure 1B). Retinal vasculitis was found in 7 eyes (58.3%). Two eyes had choroidal lesions (16.7%), of which 1 was associated with exudative retinal detachment, and another with papillitis. None of the patients had conjunctival or orbital lesions. OCT data were available for in 3 patients. The median central foveal thickness was 259 μ (range, 215-371). Cystoid macular edema was present in 2 eyes, subretinal fluid in 1 eye, and RPE irregularities in 3 eyes (Figure 1E). FA data were available in 5 patients. The most common FA findings were macular edema in 6 eyes (60%), perivascular leakage in 7 (58.3%), and no angiographic leakage in another 2 eyes (20%). There was evidence of leakage at the area of lesion in the late phases in most of the patients (Figure 1C and D). Histopathology of vitreous revealed a large cell lymphoma in 1 patient, B cell lymphoid hyperplasia in 2, and atypical lymphoid infiltration in another patient. Flow cytometric evaluation of vitreous biopsy specimen