DOI: 10.4274/tjo.galenos.2021.50607
Turk J Ophthalmol 2021;51:317-325

Case Report

Challenges in the Diagnosis of Intraocular Lymphoma

Mahmut Kaya*, Ferit Hakan Öner*, Banu Lebe**, Sermin Özkal**, Süleyman Men***, Ali Osman Saatci*

*Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
**Dokuz Eylül University Faculty of Medicine, Department of Pathology, İzmir, Turkey
***Dokuz Eylül University Faculty of Medicine, Department of Radiology, İzmir, Turkey

Abstract

Intraocular lymphomas are among the rare malignancies that present with a wide variety of clinical manifestations. Differential diagnosis can be very troublesome due to its mimicking nature, insidious disease onset, and partial treatment response to steroids. The most important step in diagnosis is a high index of suspicion. Signs of the disease are now easier to detect using multimodal imaging techniques. In this case series, we reviewed the clinical characteristics of two women aged 70 and 71 years and a 72-year-old man with intraocular lymphoma and described their multimodal imaging findings in detail. Bilateral eye involvement was present in all three cases at our first ophthalmological examination. While the disease first presented with ocular involvement in two of the three cases, ocular involvement was detected seven years after initial heart involvement in one patient. All three patients had diffuse large B-cell lymphomas (one diagnosed with retinal biopsy, one with conjunctival biopsy, and the remaining with stereotactic brain biopsy). Intraocular lymphoma should be diagnosed and treated using a multidisciplinary approach, and we share our experience in this case series.
Keywords: Eye, conjunctiva, lymphoma, optical coherence tomography, optical coherence tomography angiography, retina, retinal biopsy

Introduction

Intraocular lymphoma is a general definition that encompasses tumors that are primary or secondary to systemic (metastatic) lymphoma. The primary type includes primary vitreoretinal lymphoma and primary uveal lymphoma. Primary vitreoretinal lymphoma is a type of non-Hodgkin lymphoma with high malignancy potential that develops with or without central nervous system (CNS) involvement. The secondary type occurs as a result of systemic lymphomas invading the choroid.[1,2,3] Intraocular lymphomas account for less than 1% of all intraocular tumors and 1-2% of extranodal lymphomas.[4,5,6,7] Most primary intraocular lymphomas are primary CNS non-Hodgkin and diffuse B-cell lymphomas, though CNS involvement is observed in only 60-80% of patients.[8] Four patterns of organ involvement have been reported in intraocular lymphoma: (1) ocular and CNS (61%), (2) intraocular only (17%), (3) ocular and internal organ (17%), and (4) ocular, internal organ, and CNS (5%).[9,10]

Most patients are middle-aged or older (50-70 years) and the female to male ratio is approximately 2:1.[4] Approximately 30% of the patients have unilateral ocular involvement, while 80-90% have bilateral involvement.[6,7] The mortality risk at 12 to 36-month follow-up is 9-81%. The 5-year survival rate is less

Address for Correspondence: Ali Osman Saatci, Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
E-mail: osman.saatci@deu.edu.tr **ORCID-ID:** orcid.org/0000-0001-6848-7239
Received: 23.07.2020 **Accepted:** 03.05.2021

Cite this article as: Kaya M, Öner FH, Lebe B, Özkal S, Men S, Saatci AO. Challenges in the Diagnosis of Intraocular Lymphoma. Turk J Ophthalmol 2021;51:317-325

than 5% and tumor recurrence usually occurs within the first 3 years of diagnosis.[4,6,7]

Intraocular lymphomas almost always pose serious diagnostic and therapeutic challenges to ophthalmologists. This clinical entity, classically referred to as "uveitis masquerade syndrome," can mimic chronic uveitis in adult or older patients. However, unlike many uveitis entities, early diagnosis is crucial due to its life-threatening nature.

In this case series, we examine the presenting clinical features, multimodal images, and clinical course and prognosis of two patients with suspected intraocular lymphoma whose diagnosis was confirmed by ocular biopsy and one patient in whom cardiac lymphoma presented years later with ocular involvement.

Materials and Methods

This report includes 3 patients who presented to the retina unit of the Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology with complaints of blurred vision, reduced visual acuity, and floaters between December 2017 and March 2020. Ocular lymphoma was suspected based on the patients' ocular and systemic examination findings and the diagnosis was confirmed by histopathologic examination of a biopsy specimen. We retrospectively reviewed the records pertaining to these three cases of histopathologically diagnosed diffuse B-cell non-Hodgkin lymphoma.

Case Reports

Case 1

A 71-year-old woman presented with complaints of low vision and floaters in her left eye. The patient had undergone uncomplicated bilateral cataract surgery 8 months earlier. She reported losing vision in her right eye 2 months earlier and the onset of her current complaints in the left eye 4 days earlier. Her history of systemic disease included a 12-year history of systemic hypertension and 4-year history of moderate heart failure. She had no history of cancer.

Best corrected visual acuity (BCVA) was 0.4 in the left eye and there was no light perception in the right eye. On anterior segment examination, both eyes were pseudophakic with +2 cells in the anterior chamber and +1 cells in the anterior vitreous. Intraocular pressure was within normal limits in both eyes. Dilated fundus examination of the right eye revealed intensive vitritis, vitreous condensation, and a raised, yellow/cream-colored lesion with indistinct margins in the macular area that extended to the vascular arcades, spread below and within the retina, and was also associated with intraretinal hemorrhage (Figure 1A). In the left eye, a single large lesion was observed at the inferior vascular arcade, while in the temporal region, multiple poorly defined cream-colored deposits were observed under the retinal pigment epithelium (RPE) (Figure 1B, C). On fluorescein angiography (FA), relatively localized leakage appearing in the early phase and intensifying in the late phase was observed in the area corresponding to the lesion in the right eye (Figure 1D), while in the left eye, there were early and late hypofluorescent foci in the macula and temporal area with mild leakage from the temporal foci in the late phase (Figure 1F, G). Swept-source optical coherence tomography (SS-OCT) images could not be obtained in the right eye, while the left eye showed disruption of the outer retinal layers, multiple small pigment epithelial detachments (PED), and a hyperreflective sub-RPE lesion (possibly lymphocytic infiltration) with posterior shadowing in the temporal area (Figure 1C). SS-OCT angiography imaging was not possible in the right eye and revealed minimal vascular changes in the superficial and deep capillary plexuses and a hyporeflective area associated with infiltration in the choriocapillaris layer in the left eye. Both SS-OCT angiography and en-face imaging in the left eye showed extensive shadowing corresponding to the superficial, deep, and outer retinal and choriocapillaris layers in the inferotemporal region including the macula (Figure 2A-D). The patient was admitted to our department with a clinical prediagnosis of chronic endophthalmitis and intraocular lymphoma. Pars plana vitrectomy was performed in the right eye to rule out endophthalmitis and lymphoma and a vitreous biopsy specimen was obtained. Polymerase chain reaction (PCR) samples yielded no positive findings. Tests to rule out systemic infectious etiologies resulted negative (herpes simplex virus IgM/IgG, *Toxoplasma* IgM/IgG, cytomegalovirus IgM/IgG, venereal disease research laboratory [VDRL]/rapid plasma reagin [RPR], fluorescent treponemal antibody absorption [FTA-Abs], *Brucella*). Pulmonology consultation was requested for tuberculosis and sarcoidosis but no positive signs were detected. Brain magnetic resonance imaging (MRI) revealed no pathology except for an enhancing mass lesion adjacent to the optic disc in the right globe (Figure 2E). While the patient's examinations continued, she developed complicated retinal detachment in the right eye after core vitrectomy. With no expectation of vision in the right eye due to the complicated retinal detachment and lack of light perception, retinal biopsy and vitreoretinal surgery with silicone oil were performed after obtaining the patient's consent. The result of histopathological examination of the biopsy sample was diffuse large B-cell lymphoma (Figure 2F, G). Due to the presence of optic nerve involvement in the right eye, systemic chemotherapy and a single dose of intrathecal methotrexate were administered in the hematology unit of our hospital, and regression of the eye lesions was observed (Figure 3A, B). However, the patient died due to complications associated with systemic chemotherapy approximately 5 months after the onset of ocular complaints.

Case 2

A 70-year-old woman presented to our clinic with complaints of blurred vision in both eyes that had started 4-5 months earlier and became more pronounced in the past month. However, brain MRI performed at another center had not revealed any pathology. One month before presenting to

our clinic, she started treatment with oral methylprednisolone 32 mg/day and topical prednisolone and nepafenac at another center. She had an 8-year history of diabetes mellitus being monitored with insulin. Her BCVA was light perception in the right eye and counting fingers from 1 meter in the left eye. Anterior segment examination revealed a 3x4 mm nodular mass in the upper temporal bulbar conjunctiva (Figure 4A), chemosis and +2 cells in the anterior chamber and +1 cells in the anterior vitreous in the right eye and pseudophakia, +1 cells in the anterior chamber, and +2 cells in the anterior vitreous in the left eye. Intraocular pressures were within normal limits. On dilated fundus examination, there was dense vitritis, a mass including the macula and extending to the periphery, and exudative retinal detachment in the right eye. The left eye showed intense vitritis, exudative retinal detachment involving the macula and extending peripherally, sporadic intraretinal hemorrhages, and multiple large, yellowish cream-colored choroiditis-like lesions (Figure 4B). On FA, no image could be obtained from right eye due to severe media opacity, while mild optic disc staining and leakage from choroidal lesions in the macular and inferior area that appeared in the early phase and intensified in the late phase were observed in the left eye. Spectral-domain optic coherence tomography (SD-OCT) showed no image in the right eye and a hyperreflective lesion consistent with lymphocytic infiltration in the outer retinal layers of the left eye (Figure 4C).

Tests to rule out infectious etiologies resulted negative (herpes simplex virus IgM/IgG, *Toxoplasma* IgM/IgG, cytomegalovirus IgM/IgG, VDRL/RPR, FTA-Abs, *Brucella*). Pulmonology consultation for tuberculosis and sarcoidosis yielded no positive signs for these conditions. For the differential diagnosis of endogenous endophthalmitis and intraocular lymphoma, diagnostic vitrectomy to obtain a vitreous biopsy sample was performed twice in the right eye and once in the left eye. In the same session as the biopsy, intravitreal 1 mg/0.1 mL vancomycin, 2.25 mg/0.1 mL ceftazidime, and 0.4 mg/0.1 mL dexamethasone injections were administered for suspected infectious endophthalmitis. No bacteria, yeast, or hyphae were observed on direct examination; bacterial and fungal cultures were negative. No atypical cells were observed in the cytological examination for lymphoma and no positive results were obtained on PCR. No enhancing focus was detected by positron emission tomography. The patient's visual complaints increased, and a Tenon-conjunctival biopsy specimen was obtained from the nodular mass in the right superotemporal bulbar conjunctiva. The pathology report indicated diffuse large B-cell lymphoma (Figure 4D, E). After diagnosis, intravitreal 400 µg/0.1 mL methotrexate was administered twice to the right eye and once to the left eye in addition to systemic therapy.

A second brain MRI performed 1 month after histopathological diagnosis due to the onset of altered consciousness, malaise,

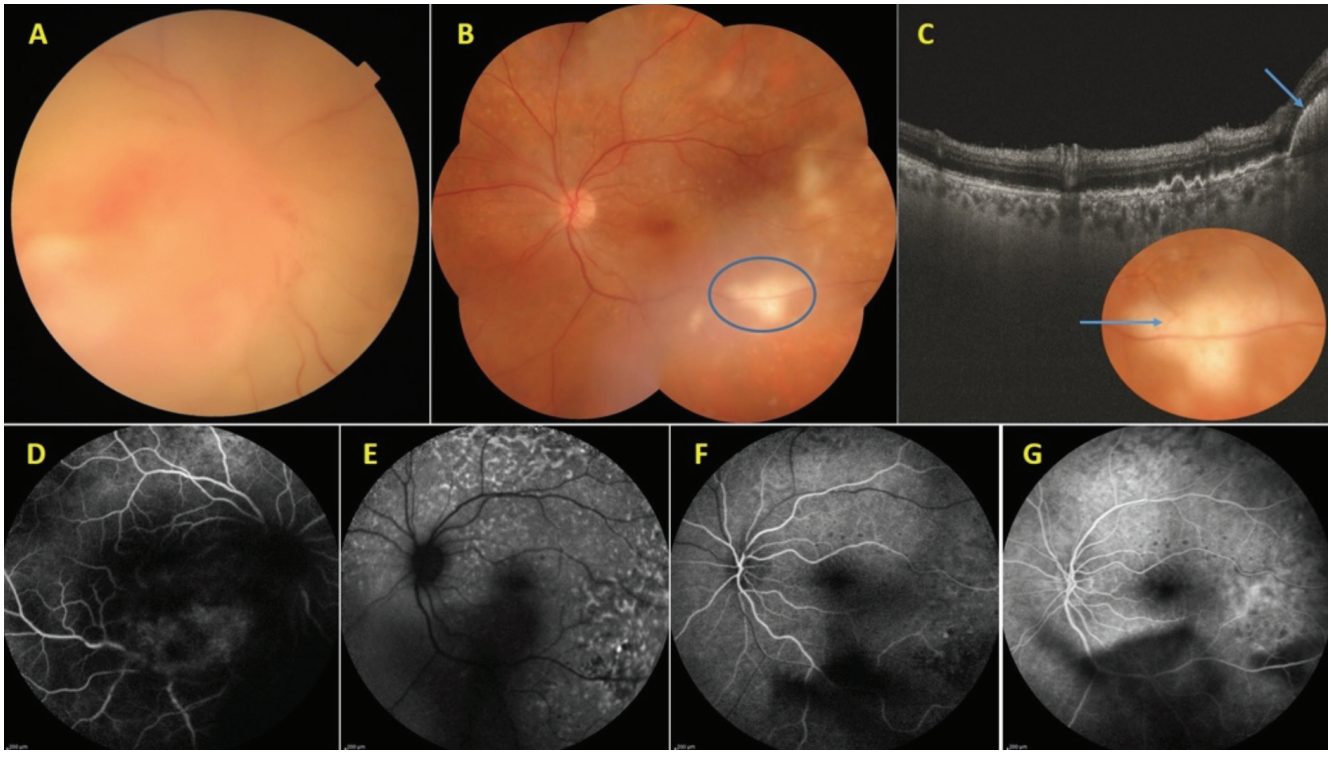

Figure 1. Patient 1. Color fundus images show intense vitritis and intraretinal and subretinal yellowish cream-colored lymphoma infiltration filling the macular area in the right eye (A) and multifocal sub-retinal pigment epithelium (RPE) lesions suspected to be infiltrative in the left eye (B and C, blue circle/arrows). Fluorescein angiography of the right eye showed regional leakage appearing in the early phase and intensifying in the late phase (D). In the left eye, fundus autofluorescence imaging revealed multifocal hyperautofluorescent spots (E) and fluorescein angiography showed early and late hypofluorescent foci in the macula and temporal area (F, G)

vomiting, and headache revealed widespread CNS lymphoma. The patient died of CNS lymphoma approximately 12 months after the onset of ocular complaints.

Case 3

A 72-year-old man presented to our clinic with complaints of low vision in his right eye. His medical history included a diagnosis of diffuse cardiac large B-cell lymphoma 7 years earlier. He reported having no problems in routine follow-up after chemotherapy and stem cell transplantation. On ophthalmologic examination performed at admission, BCVA was counting fingers at 1 meter in the right eye and 0.8 in the left eye. No pathology other than bilateral 2+ nuclear sclerosis was detected on biomicroscopic examination. Intraocular pressure was 24 mmHg in the right eye and 23 mmHg in the left eye. Fundus examination revealed vitreous turbidity (+2 vitritis) and a large, poorly defined, yellow/cream-colored subretinal choroidal lesion in the macular temporal region in the right eye and drusen-like small white spots in the posterior pole of the left eye (Figure 5A, C). SD-OCT showed subretinal fluid in the right eye and disruption of the outer retinal layers, multiple small PEDs and hyperechogenicity, and drusen-like structures in the left eye (Figure 5B, D). On FA, multiple leaks appearing in the early

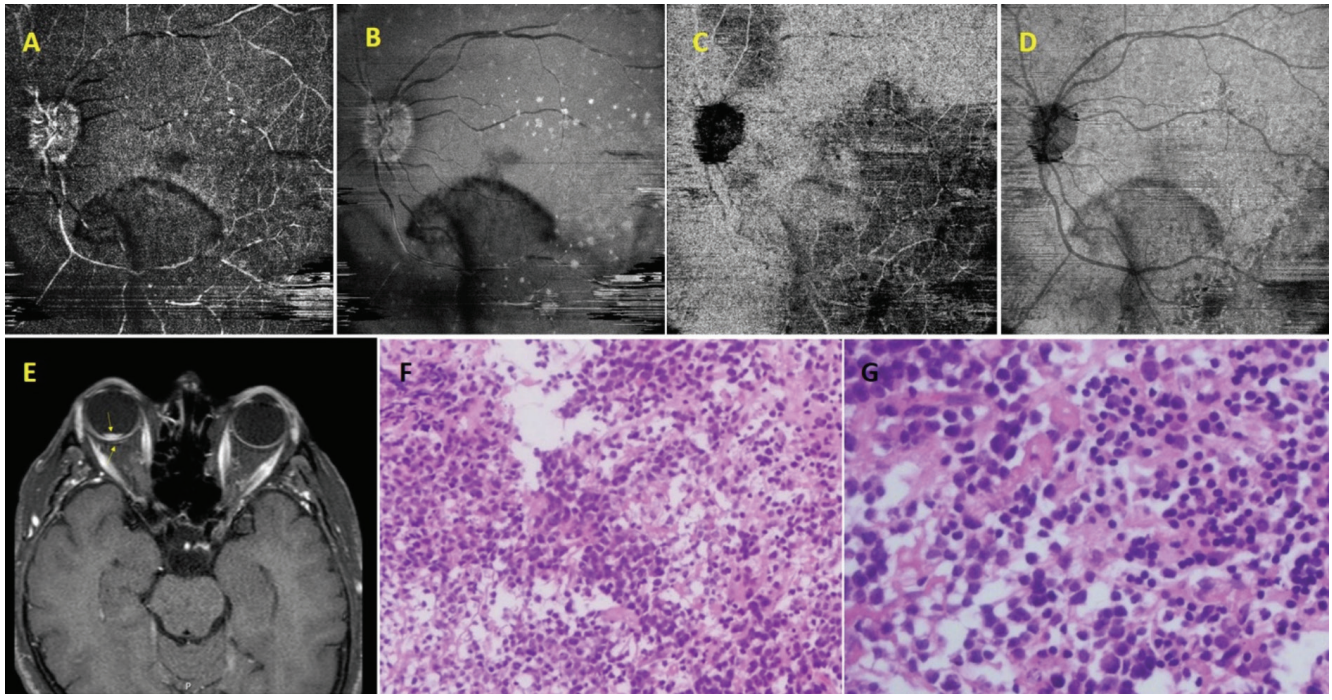

Figure 2. Patient 1. On swept-source optical coherence tomography angiography (12x12 mm), deep capillary plexus and corresponding en face images showed a hyporeflective area approximately 3 disc diameters in size in the macular area corresponding to the subretinal/intraretinal lymphocytic infiltration and multifocal hyperreflective spots in the macular area (A-C). In choriocapillaris layer and corresponding en face images, the lymphocytic infiltration appeared as a larger hyporeflective area with multifocal hyporeflective spots (B,-D). Brain magnetic resonance imaging revealed an enhancing mass lesion adjacent to the optic disc in the posterior pole of the right eye (E, yellow arrows). Retinal biopsy showed intense infiltration of large lymphoid cells containing atypical nuclei (right eye, hematoxylin-eosin, x200 [F] and x400 [G])

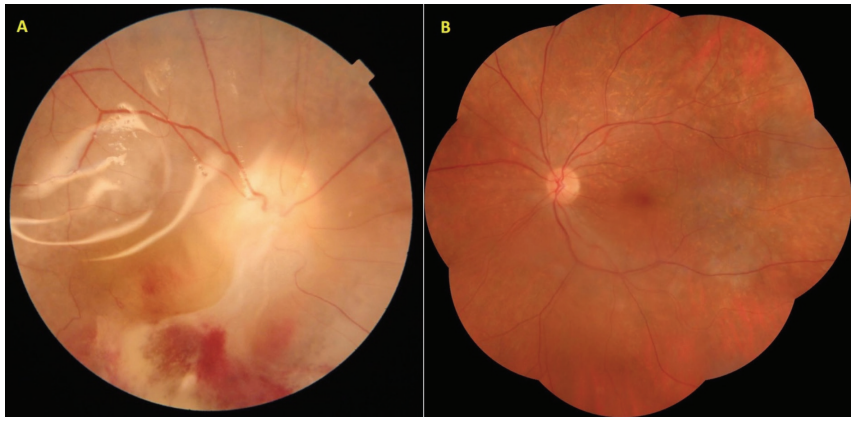

Figure 3. Patient 1. During treatment, color fundus images showed regression of the mass and lesion foci in the right and left eyes (A, B)

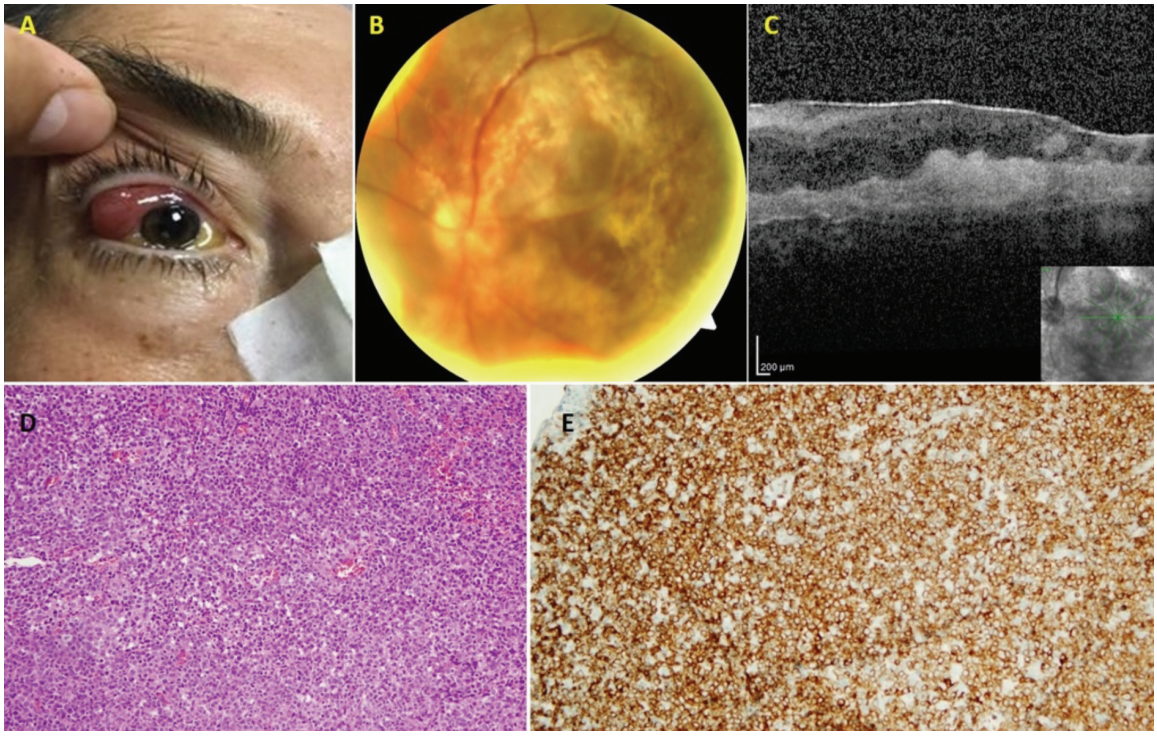

Figure 4. Patient 2. Anterior segment examination showed a pronounced conjunctival lymphoma infiltration in the superotemporal area of the right eye (A). Color fundus image of the left eye showed a yellowish cream-colored lymphoid mass that filled the macular area and extended past the vascular arcades (B). On spectral-domain optical coherence tomography, a cross-section through the lesion in the left eye revealed a hyperreflective lesion suspected to be lymphocytic infiltration in the outer retinal layers (C). Tenon-conjunctival biopsy of the superotemporal nodular conjunctival mass in the right eye showed atypical lymphoid cells in the lamina propria and infiltrating the conjunctival epithelium (D, hematoxylin-eosin x200). On immunohistochemical examination, diffuse cell distribution was observed in CD20 antibody staining (E)

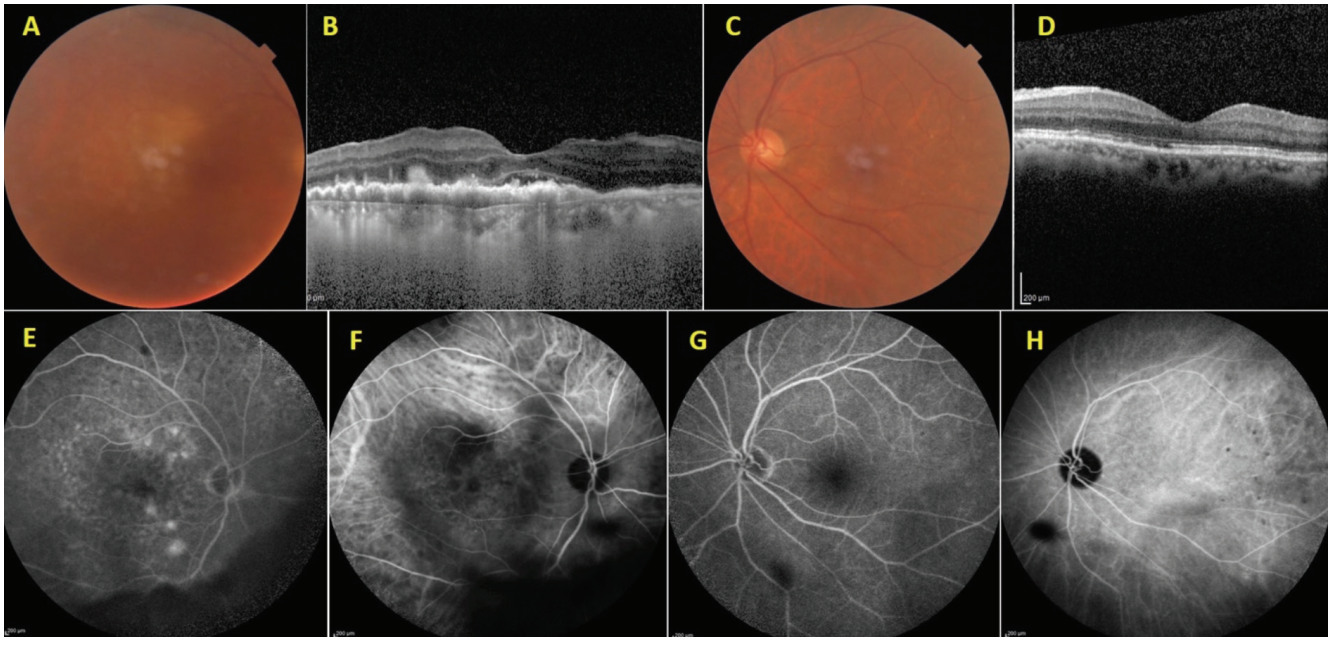

Figure 5. Patient 3. Color fundus images showed mild vitritis and multifocal yellowish cream-colored intraretinal and subretinal lymphoma infiltration up to 2-3 disc diameters in size in the temporal macula in the right eye (A) and multifocal, well-defined drusen-like lesions in the temporal macula in the left eye (C). Spectral domain optical coherence tomography showed subretinal fluid and a hyperreflective lesion thought to be intense lymphocytic infiltration in the choroidal, subretinal, and outer retinal layers of the right eye (B) and a hyperreflective drusen-like lesion thought to be lymphocytic infiltration at the retinal pigment epithelium and ellipsoid zone level (D). On fluorescein angiography, late hyper- and hypofluorescence spots and leakage were observed in the right and left eyes (E-G). Indocyanine green angiography revealed hypofluorescent spots that were extensive in the right eye but appeared only in the temporal area in the left eye (F-H)

phase and intensifying in the late phase were observed in the macula in the right eye, while no significant leakage was observed in the left eye (Figure 5E, G). Indocyanine green angiography (ICGA) revealed well-defined areas of hypofluorescence in the macula and peripheral retina of the right eye and the temporal area of the left eye (Figure 5F, H). SS-OCT angiography showed minimal vascular changes in the superficial and deep capillary plexuses in the right eye and no pathology in the left eye. In the right eye, both SS-OCT angiography and en-face imaging showed extensive shadowing from the lesions in the macula and temporal region in the area corresponding to the corresponding to the superficial, deep, and outer retinal and choriocapillaris layers, while the left eye showed multiple hyperreflective lesions corresponding to only the choriocapillaris layer (Figure 6A-H).

On cranial computed tomography, a hyperdense mass lesion arising from the left frontal lobe gyrus rectus and causing vasogenic edema was observed in axial precontrast and postcontrast sections (Figure 6I). The lesion's isodensity to gray matter in precontrast examination and strong homogeneous enhancement in postcontrast examination were considered typical for lymphomatous involvement. At the patient's request, he was referred with a detailed discharge report back to the other university clinic where he had been followed previously for cardiac lymphoma. In a telephone follow-up with the patient, he reported that diagnostic stereotactic brain biopsy of the lesion had been performed in the neurosurgery department and the pathology results were consistent with lymphoma.

Discussion

The diagnostic features of primary intraocular lymphoma were determined according to the International Primary CNS Lymphoma Group.[11] These are: (a) age 50 years and older in most patients, (b) painless vision loss and floaters, (c) bilateral eye involvement, initially monocular involvement in some cases, (d) different types of keratic precipitates, and (e) although uncommon, scleritis, pseudohypopyon, hyphema, and anterior and posterior synechiae. Vitreous cell infiltration is generally observed, appearing as large cells in characteristic streaks in the anterior vitreous. Cell clusters in the vitreous should arouse suspicion of lymphoma, but snow banking, vitreous hemorrhage, and retinal holes are not among the expected findings in lymphoma. Multifocal cream/yellow-white lesions with tendency to confluence in the outer retinal layers or under the RPE, leopard-spot retinal lesions, RPE atrophy, and fibrosis should also raise suspicion for lymphoma. Retinal hemorrhage, retinal vasculitis, macular edema, retinal detachment, and necrotizing retinitis can be seen in advanced stages of disease.[11] Anterior synechiae and iris depigmentation hardly ever occur in these patients. In all three cases presented here, the diagnostic features summarized by the International Uveitis Study Group were also taken into consideration and intraocular lymphoma was suspected during their initial admission examinations.

Intraocular lymphomas are rare malignancies with highly variable clinical manifestations; therefore, differential diagnosis is quite difficult. Delayed diagnosis is common because it has an insidious onset, mimics other uveitis entities, and shows an initial partial response to steroid therapy. In these patients, the disease can often be clinically masked by chronic uveitis and vitritis of unknown cause.[3,6,12] The differential diagnosis of lymphoma should include benign reactive lymphoid hyperplasia of the uvea, systemic non-Hodgkin lymphoma, metastatic tumors, amelanotic melanoma, and uveitic entities. Infectious and inflammatory uveitis entities include endogenous endophthalmitis, toxoplasmosis, acute retinal necrosis, cytomegalovirus retinitis, syphilis, tuberculosis, sarcoidosis, acute posterior multifocal plaque pigment epitheliopathy, multifocal choroiditis, and birdshot chorioretinopathy.[12] The

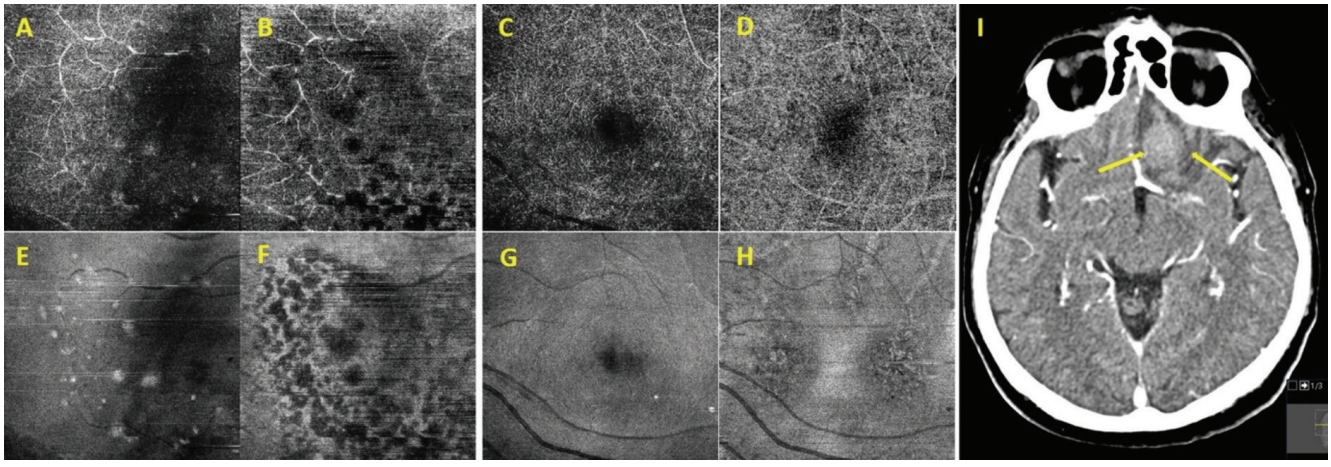

Figure 6. Patient 3. On swept-source optical coherence tomography angiography (6x6 mm), deep capillary plexus and corresponding en face images in the right eye showed multifocal hyperreflective spots corresponding to the choriocapillaris/subretinal/intraretinal lymphocytic infiltration (A, E). In choriocapillaris layer and compatible en face images, the lymphocytic infiltration appeared as a larger hyporeflective area with multifocal confluent hyporeflective spots (B, F). In the left eye, deep capillary plexus and corresponding en face images showed several hyperreflective spots (C, G) and choriocapillaris layer and corresponding en face images showed clusters of multifocal hypo- and hyperreflective spots consistent with lymphocytic infiltration in the macular area (D, H). On brain computed tomography, post-contrast axial sections revealed a hyperdense mass lesion arising from the left frontal lobe gyrus rectus causing adjacent vasogenic edema (I, yellow arrows)

key to early diagnosis of intraocular lymphoma is clinical suspicion. In ophthalmological examination, characteristic findings on multimodal imaging reinforce the suspicion of intraocular lymphoma. In our case series, although lymphoma was initially suspected in patient 2 based on clinical findings of bilateral chronic vitritis that did not respond to treatment, the negative results in cytologic examination of vitreous specimens led to a late diagnosis. Considering endogenous endophthalmitis due to uncontrolled diabetes mellitus, vitreous culture was performed and the patient was treated with intravitreal 1 mg/0.1 mL vancomycin, 2.25 mg/0.1 mL ceftazidime, and 0.4 mg/0.1 mL dexamethasone at regular intervals. However, the vitreous culture was negative. As the patient did not respond to treatment for endophthalmitis and enlargement of the conjunctival mass was observed, a conjunctival biopsy of the nodular mass was performed and enabled the diagnosis of intraocular lymphoma. In most cases reported in our country, a definitive diagnosis was made by brain biopsy. The demographic and clinical characteristics and definitive diagnostic methods of intraocular lymphoma patients reported in the literature from our country are summarized in Table 1.

Although a definitive diagnosis of intraocular lymphoma is made histopathologically, some multimodal fundus imaging findings are typical.[12,13,14,15,16,17,18,19,20,21,22] On fundus examination and color fundus photography, vitreous opacification may be seen due to lymphoma cell infiltration, but most cases present with typical yellowish-white irregular lesions that form in the outer retinal layers and/or under the RPE due to infiltration and tend to merge and expand. The characteristic brownish pigment accumulation in the yellowish-white lesions causes the specific leopard-spot pattern seen in intraocular lymphoma. The yellowish-white lesions in the outer retinal layers and under the RPE may shrink with treatment or atrophy over time without treatment. Although FA findings are not characteristic, some typical findings include round or well-defined hypofluorescent lesions in the early and late phases resulting from blockade by the sub-RPE infiltrative lesion, as well as granular hyperfluorescence and late staining due to RPE irregularity. Less frequently, there may be signs of vasculitic and cystic macular edema. In fundus autofluorescence imaging, confluent punctate appearance or granular hyper- and hypoautofluorescence pattern is a characteristic finding of lymphoma. On SD-OCT, nodular hyperreflective lesions at the RPE level and sub-RPE lesions between the RPE and Bruch's membrane can be observed in the early stage of the disease. In the later stages of the disease, "wave-like" turbulence may occur between the RPE and Bruch's membrane.[23] On ICGA imaging, lymphoma infiltration is less useful in diagnosis due to its intraretinal and/or subretinal location and generally appears as round clusters of hypofluorescent lesions.[17,22] On en face OCT angiography imaging, subretinal nodular infiltrates appear in a granular hyper- and hyporeflective pattern while large lesions are hyporeflective.[24] FA and ICGA findings have a positive predictive value of 89% and negative predictive value of 85% for intraocular lymphoma.[22] In our three cases, multimodal imaging findings strongly suggested intraocular lymphoma. However, under the current conditions, in our country as well as in other countries, systemic lymphoma treatment cannot be initiated without histopathological confirmation of the diagnosis. The diagnosis and treatment of intraocular lymphoma requires a multidisciplinary team. In the treatment of intraocular lymphoma, a professional team of ophthalmologists and oncologists (especially specialists in neuro-oncology or hematology) is necessary to optimize patient management.

In cases of suspected intraocular lymphoma, methods to employ in etiological studies include cranial imaging methods, lumbar puncture, cytological examination of cerebrospinal fluid, and if these are inconclusive, vitreous biopsy and chorioretinal biopsy.[1,2,3,4,5,6,7,8] A study from the National Eye Institute found that an average of 2.1 procedures (pars plana vitrectomy, vitreous fluid sampling, anterior chamber fluid sampling, chorioretinal biopsy, brain biopsy, and cerebral aneurysm fluid sampling) were used to diagnose vitreoretinal lymphoma.[25] It was reported that ocular cytokine analysis of the vitreous fluid in patients with intraocular lymphoma shows higher levels of interleukin (IL)-10 than IL-6 (IL-10 to IL-6 ratio >1.0).[26] This molecular test is useful in the differential diagnosis of inflammatory conditions. However, as this method is not routinely used in every center in our country, diagnosis is more challenging than in developed countries. The demonstration of malignant lymphocytes in vitreous samples is the most definitive method for the diagnosis of intraocular lymphoma. The positive predictive diagnostic value of cytologic examination of a vitreous sample varies between 30% and 50%.[27] In the literature, it is emphasized that rapid cytolysis of tumor cells in the vitreous may make diagnosis difficult and repeated diagnostic vitrectomies may be required. Diagnostic vitrectomy should be done using a 25-gauge (G) system at a low cutting speed (up to 1,500 cuts per minute) to minimize destruction of infiltrative cells and 0.5-1 mL of undiluted vitreous should be obtained before turning on the infusion fluid. If diagnostic vitrectomy is planned for a patient using systemic steroids, they should be discontinued at least 2 weeks in advance if possible.[26] In cases where vitreous sampling is inadequate for diagnosis, retinal biopsy is an invasive method that provides more viable tumor cells. Of our cases, retinal biopsy was performed in patient 1 shortly after obtaining a cytologically negative vitreous sample and the diagnosis of intraocular lymphoma was confirmed by detecting malignant lymphocyte cells in the biopsy specimen. In patient 2, diagnosis was delayed by negative results from two separate cytology samples obtained from the vitreous. In contrast, when patient 3 developed visual complaints with a history of cardiac lymphoma, secondary intraocular lymphoma was presumed based on ophthalmological examination and multimodal imaging, and the diagnosis was confirmed by brain biopsy of a lesion detected on brain MRI at another center.

Table 1. Cases of intraocular lymphoma reported in Turkey

Author (year, reference no)	Gender, age	Affected eye	Initial site of involvement	Uveitis masquerade syndrome	Vitreous biopsy	Definitive diagnosis	Time from presentation to definitive diagnosis	Prognosis
Ateş et al.[14]								
Case 1	F, 22	Bilateral	Systemic	-	-	Abdominal biopsy	<1 month	Under follow-up
Uysal et al.[15]								
Case 1		Right	Intraocular	+	+	Chorioretinal biopsy	<1 month	Under follow-up
Sürenkök et al.[16]								
Case 1	F, 68	Right	Intraocular	-	+	Retinal biopsy	2 months	Death
Saatci et al.[17]								
Case 1	M, 35	Bilateral	Systemic	-	-	Axillary lymph node biopsy	<1 month	Under follow-up
Tugal-Tutkun et al.[18]								
Case 1	F, 60	Bilateral	Intraocular	-	+	Vitreous biopsy	1.5 months	Under follow-up
Case 2	M, 32	Right	CNS	-	-	Brain biopsy	-	Under follow-up
Case 3	M, 38	Bilateral	CNS	+	-	Brain biopsy	<1 month	Undergoing treatment
Yüksel et al.[19]								
Case 1	F, 60	Bilateral	Intraocular	+	-	?	-	Death
Case 2	M, 58	Bilateral	Intraocular	+	+ (twice)	Brain biopsy	3-4 months	Undergoing treatment
Demir et al.[20]								
Case 1	M, 75	Bilateral	Intraocular	+	+	Brain biopsy	?	Under follow-up
Present study (2021)								
Case 1	F, 71	Bilateral	Intraocular	-	+	Retinal biopsy	2 months	Death
Case 2	F, 70	Bilateral	Intraocular	-	+ (twice)	Conjunctival biopsy	10 months	Death
Case 3	M, 72	Bilateral	Systemic	-	-	Brain biopsy	3 months	Undergoing treatment

F: Female, M: Male, CNS: Central nervous system

In conclusion, the differential diagnosis of intraocular lymphoma is challenging. The first step toward early diagnosis is clinical suspicion. If suspected, characteristic findings that support the diagnosis can be detected with multimodal imaging methods. As ocular involvement may be the first clinical presentation, cranial imaging should also be performed due to possible CNS involvement. In patients with suspected intraocular lymphoma, vitreous biopsy and in some cases retinal biopsy is necessary for a definitive diagnosis and subsequent oncological treatment.

Ethics

Informed Consent: Obtained.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.K., F.H.Ö., A.O.S, Concept: M.K., A.O.S., Design: M.K., A.O.S., Data Collection or Processing: M.K., Analysis or Interpretation: M.K., F.H.Ö., B.L., S.Ö., S.M., A.O.S., Literature Search: M.K., A.O.S., Writing: M.K., B.L., S.M., A.O.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Buggage RR, Chan CC, Nussenblatt RB. Ocular manifestations of central nervous system lymphoma. Curr Opin Oncol. 2001;13:137-142.
2. Fredrick DR, Char DH, Ljung BM, Brinton DA. Solitary intraocular lymphoma as an initial presentation of widespread disease. Arch Ophthalmol. 1989;107:395-397.
3. Chan CC, Rubenstein JL, Coupland SE, Davis JL, Harbour JW, Johnston PB, Cassoux N, Touitou V, Smith JR, Batchelor TT, Pulido JS. Primary vitreoretinal lymphoma: a report from an international primary central nervous system lymphoma collaborative group symposium. Oncologist. 2011;16:1589-1599.

4. Reichstein D. Primary vitreoretinal lymphoma: an update on pathogenesis, diagnosis and treatment. Curr Opin Ophthalmol. 2016;27:177-184.
5. Reddy EK, Bhatia P, Evans RG. Primary orbital lymphomas. Int J Radiat Oncol Biol Phys. 1988;15:1239-1241.
6. Mochizuki M, Singh AD. Epidemiology and clinical features of intraocular lymphoma. Ocul Immunol Inflamm. 2009;17:69-72.
7. Tang LJ, Gu CL, Zhang P. Intraocular Lymphoma. Int J Ophthalmol. 2017;10:1301-1307.
8. Freeman LN, Schachat AP, Knox DL, Michels RG, Green WR. Clinical features, laboratory investigations, and survival in ocular reticulum cell sarcoma. Ophthalmology. 1987;94:1631-1639.
9. Pe'er J, Hochberg FH, Foster CS. Clinical review: treatment of vitreoretinal lymphoma. Ocul Immunol Inflamm 2009;17:299-306.
10. Dalvin LA, Lim LS, Ancona-Lezama D, Mazloumi M, Chang M, Porcu P, Martinez NL, Glass J, Mashayekhi A, Shields CL. Clinical Features Predictive of Survival in Patients With Vitreoretinal Lymphoma: Analysis of 70 Patients at a Single Ocular Oncology Center. Asia Pac J Ophthalmol (Phila). 2020;9:110-116.
11. Chan CC, Rubenstein JL, Coupland SE, Davis JL, Harbour JW, Johnston PB, Cassoux N, Touitou V, Smith JR, Batchelor TT, Pulido JS. Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma Collaborative Group symposium. Oncologist. 2011;16:1589-1599.
12. Chan CC, Wallace DJ. Intraocular lymphoma: update on diagnosis and management. Cancer Control. 2004;11:285-295.
13. Davis JL, Miller DM, Ruiz P. Diagnostic testing of vitrectomy speciments. Am J Ophthalmol. 2005;140:822-829.
14. Ateş Y, Yakarcan M, Oktay F, Kaynak S, Payzın B. Oküler Tutulumlu Bir Non-Hodgkin Lenfoma Olgusu. Ret-Vit. 2001;9:64-69.
15. Uysal Y, Sobacı G, Sefalı M, Bayraktar MZ. Koryoretinal Biyopsi ile Tanı Konan Primer İntraoküler Lenfoma. Ret-Vit (Özel Sayı). 2003;11:1-7.
16. Sürenkök S, Oysul K, Beyzadeoğlu M, Özet A. İntraoküler yerleşimli Non-Hodgkin lenfoma, bir olgu raporu ve literatürün gözden geçirilmesi. Türk Onkoloji Dergisi. 2009;24:48-52.
17. Saatci AO, Arikan G, Ozcan MA, Ozkal S, Kargi A, Undar B. Indocyanine green angiographic features of systemic non-Hodgkin's lymphoma and bilateral choroidal involvement. Ophthalmic Surg Lasers Imaging. 2006;37:236-239.
18. Tugal Tutkun İ, Yıldırım Ö, Kır N. Santral Sinir Sistemi Tutulumu ile Birlikte Primer İntraoküler Lenfoma. Turk J Ophthalmol. 2008;38:242-249.
19. Yüksel E, Özdek Ş, Yüksel N, Korkmaz Ş, Hasanreisoğlu H. Panüveitli Multifokal Koroiditi Taklit Eden İntraoküler Lenfoma. Turk J Ophthalmol. 2010;40:46-50.
20. Demir MN, Sungur G, Gürelik İG, Özkan G, Bitik B, Ünlü N, Acar MA. İmmünsupresif tedavi Sonrası İntraoküler Tüberküloz ve Lenfoma. Ret-Vit. 2017;26:169-174.
21. Cassoux N, Merle-Beral H, Leblond V, Bodaghi B, Miléa D, Gerber S, Fardeau C, Reux I, Xuan KH, Chan CC, LeHoang P. Ocular and central nervous system lymphoma: clinical features and diagnosis. Ocul Immunol Inşamm. 2000;8:243-250.
22. Fardeau C, Lee CP, Merle-Béral H, Cassoux N, Bodaghi B, Davi F, Lehoang P. Retinal şuorescein, indocyanine green angiography, and optic coherence tomography in non-Hodgkin primary intraocular lymphoma. Am J Ophthalmol. 2009;147:886-894.
23. Shields CL, Arepalli S, Pellegrini M, Mashayekhi A, Shields JA. Choroidal lymphoma shows calm, rippled, or undulating topography on enhanced depth imaging optical coherence tomography in 14 eyes. Retina. 2014;34:1347-1353.
24. Toledo JJ, Asencio M, García JR, Morales LA, Tomkinson C, Cajigal C. OCT Angiography: Imaging of Choroidal and Retinal Tumors. Ophthalmol Retina. 2018;2:613-622.
25. Dalal M, Casady M, Moriarty E, Faia L, Nussenblatt R, Chan CC, Sen HN. Diagnostic procedures in vitreoretinal lymphoma. Ocul Immunol Inflamm. 2014;22:270-276.
26. Sugita S, Takase H, Sugamoto Y, Arai A, Miura O, Mochizuki M. Diagnosis of intraocular lymphoma by polymerase chain reaction analysis and cytokine profiling of the vitreous fluid. Jpn J Ophthalmol. 2009;53:209-214.
27. Davis JL, Miller DM, Ruiz P. Diagnostic testing of vitrectomy speciments. Am J Ophthalmol. 2005;140:822-829.