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Original Article

Retrospective Evaluation of Clinical, Demographic, and Radiological Data of Orbital Lymphoma Patients: A Single Tertiary Center Experience

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Abstract

Objectives: The objective of the study was to present different clinical presentations, clinical and histopathological features, and treatment outcomes of intraorbital lymphoma.

Methods: Medical records of 18 eyes of 17 patients with histopathologically proven diagnoses of intraorbital lymphoma at Dokuz Eylül University Ophthalmology Department, between 2007 and 2022, were reviewed retrospectively. The age, gender, location, laterality, stage, type of involvement, histopathological features, systemic involvement, recurrence, time from initial symptoms to diagnosis, follow-up time, and survival times were recorded. Visual acuities at the time of diagnosis and following treatment were evaluated.

Results: The mean age of the patients was 63±19.11 (range: 15–79, median age 65). The most common presenting findings were periorbital swelling, conjunctival mass, and ptosis. Periorbital region involvement was present in 10 of 17 cases (58.8%) and conjunctival involvement was present in 7 cases (41.2%). Biopsy samples were taken from all cases. Non-Hodgkin lymphoma was the most common type of lymphoma, whereas the most common histopathological diagnoses were marginal zone lymphoma and diffuse large B-cell lymphoma. One case was diagnosed with mature T-cell lymphoma. Nine cases had bone marrow involvement. While two cases refused treatment, two cases were not treated due to age and comorbid diseases. Nine cases received chemotherapy, two cases received radiotherapy (RT), 1 case received chemotherapy and RT, and one case received antibiotherapy treatment. In one case with proptosis and exposure keratitis, lateral canthatomy, temporary tarsorrhaphy, and aggressive topical treatment resulted in complete epithelialization of the cornea.

Conclusion: Orbital lymphoma is a painless and slowly progressive clinical picture that requires high clinical suspicion because it is a common tumor of the orbit. Although clinical symptoms and findings vary according to the intraorbital location of lymphoma, patients should be examined for systemic involvement and followed up in a multidisciplinary manner.

Keywords: Intraorbital lymphoma, lymphoma, orbit, orbital lymphoma

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Introduction

Lymphoma is the most common malignant tumor of the orbit. "Orbital lymphoma" refers to intraorbital and ocular surface lymphomas (i.e., conjunctiva, eyelid, and lacrimal gland). Although it was seen as a rare case in the 1st years of its definition, its frequency has increased with the development of diagnostic technologies over time. Orbital lymphoma accounts for approximately 10% of all orbital tumors and approximately 2% of all nodal and extra-nodal lymphomas (1-5). Orbital lymphoma treatment varies depending on the type of underlying disease. Accordingly, treatment options include the "watchful wait strategy," surgery, radiotherapy (RT), chemotherapy, immunotherapy, and chemoimmunotherapy (1,6-8).

Clinical suspicion is important for the early diagnosis of the disease. Quick differential diagnosis and early referral to relevant disciplines are ocular and vital emergencies.

Herein, we retrospectively analyzed the clinical features, treatment, and disease course of patients admitted to our clinic with different signs and symptoms and were subsequently diagnosed with orbital lymphoma.

Methods

Study Design and Patient Selection

We retrospectively searched the medical records for patients diagnosed with orbital lymphoma. A retrospective case series analysis revealed 17 patients admitted to the Dokuz Eylül University Ophthalmology Department between 2007 and 2022 and were subsequently histologically diagnosed with orbital lymphoma. Experienced pathologists confirmed orbital lymphoma diagnosis and determined histological subtypes using the 2016 revision of the World Health Organization classification of lymphoid neoplasms on biopsy or surgical samples (9). The age, gender, location, laterality, stage, type of involvement, histopathological features, systemic involvement, recurrence, diagnosis, follow-up, and survival times of the patients were examined. The patients' visual acuities at the time of diagnosis and after treatment were examined. Patients with intraocular involvement were excluded from the study. This study was approved by the Ethical Committee of Dokuz Eylül University (2022/23–18) and was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and local regulations.

Radiological imaging findings were reviewed from our institution's Picture Archiving and Communication Systems archive. Images were available for 15 of the 17 patients. Fourteen patients had orbital and brain magnetic resonance imaging (MRI), including diffusion-weighted imaging (DWI). One patient with a pacemaker could not undergo magnetic resonance scanning, so the patient was monitored by computed tomography (CT) imaging. Seven patients had positron emission tomography (PET) CT scanning of the whole body at the time of diagnosis. Ten patients had orbital CT scanning.

An experienced radiologist calculated the tumor sizes of the patients. The tumor volume was calculated using the ellipsoid formula, multiplying the largest anteroposterior (height), transverse (width), and cephalocaudal (length) tumor diameters by 0.524 (height × width × length × π/6) (10). The tumor volume was measured on the radiologic images initially and during the follow-up to monitor the tumor size as a response to treatment.

On consultation with the hematology department, a treatment plan was created based on the patients' clinical, laboratory, histopathological, and radiological findings. Treatment plans included "watchful wait strategy," surgical excision, RT, anti-biotherapy, immunotherapy, and chemoimmunotherapy.

Results

A total of 18 eyes of 17 patients were included in the study. The mean age of the patients was 63±19.11 years (15–79, median: 65). Only one patient was at the pediatric age (i.e., 15 years old). Four patients (23.5%) were female, and 13 were male (76.5%). The time from initial symptoms to diagnosis of the patients was 7.76±13.99 months (1–60).

Periorbital involvement was present in 10 patients, whereas conjunctival involvement was present in seven patients. Findings at presentation were periorbital swelling in 10 patients, conjunctival mass in seven patients, ptosis in three patients, proptosis in one patient, hypoglobus in one patient, chemosis in one patient, epiphora in one patient, and exposure keratitis in one patient (Figs. 1-3 and Table 1).

Comprehensive abdominal ultrasound, PET-CT, or neck, thorax, orbit, abdomen, and pelvic CT scans were performed. After hematology and oncology consultations, all patients were diagnosed with "primary orbital lymphoma". The masses were only extraconal in 11 patients, intraconal and extraconal in two patients, only intraconal in one patient, and on the eyelid in one patient. In one patient, the extraconal part of the mass extruded through the inferior orbital rim and extended to the infraorbital region. In one patient, the lesion involved the conjunctiva in a plaque-like fashion. There was an intraocular and separate extraconal mass in another patient. The volume of the masses ranged from 0.1 mL to 43 mL (mean 9.03 mL). The mass caused proptosis in most patients,

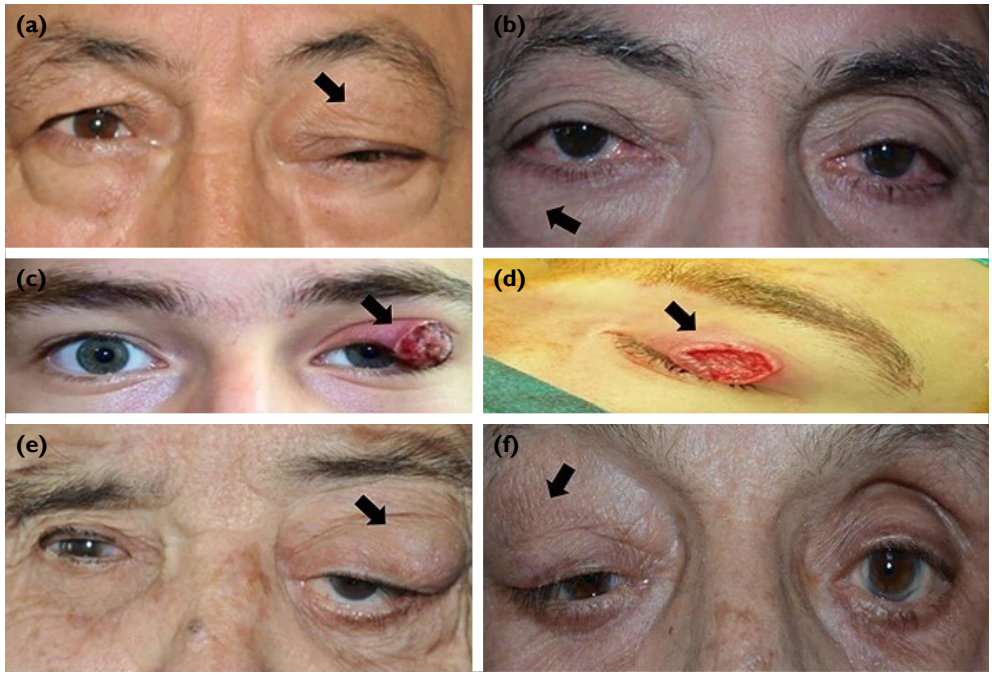

Figure 1. Sample of adnexal lymphoma cases. **(a)** Periorbital swelling and ptosis in the left eye. **(b)** Periorbital swelling and proptosis in the right eye. **(c, d)** Preoperative and intraoperative mass on the eyelid in the left eye. **(e)** Conjunctival mass, periorbital swelling, and hypoglobus in the left eye. **(f)** Periorbital swelling and ptosis in the right eye. (Black arrows indicate lesions.)

proportional to its size. The masses rarely had a particular shape; rather, they grew by replacing the orbital fat tissue and passing around barriers such as extraocular muscles, eyeballs, or the optic nerve sheath. The tumor tended to wind around or slightly push intraorbital structures like muscles.

In almost all patients, the mass was hypointense on T1-weighted (T1W) images and showed strong and homogenous enhancement on post-contrast T1W images. On T2W images, the mass had a signal intensity similar to white matter. Similarly, the tumor's apparent diffusion coefficient (ADC) values were close to the white matter ADC values. On CT, the mass was isodense to the brain cortex. In seven patients who underwent PET scanning, increased fluorodeoxyglucose (FDG) activity was noted in the orbital mass.

The follow-up imaging was done in 15 patients with various periods that ranged from 2 months to 15 years (mean 4.3 years). The masses radiologically disappeared totally or almost totally in the follow-up period in 10 patients. In one patient, the mass disappeared after treatment; however, it recurred in the contralateral orbit 11 years later. The recurrent mass disappeared, and no further recurrence was observed in the subsequent 4 years. There was a local recurrence in one patient 1 year after treatment. Remission was achieved in 1 year, and no recurrence was seen in the following 7 years. The mass was still present in the 2nd and 3rd months of follow-up in two patients at the end of the study. One patient died in 7 months, and the mass never vanished.

Ten patients (58.8%) had marginal zone lymphoma, 5 patients (29.4%) had diffuse large B-cell lymphoma (DLBCL), 1 patient (5.9%) had small lymphocytic lymphoma (SLL), and 1 patient (5.9%) had mature T-cell lymphoma, as per the histopathological features. Nine patients (52.9%) had systemic involvement, including bone marrow involvement, at the time of diagnosis.

The mean follow-up of the patients was 76.88±55.77 months, with 12 of the 17 patients following for at least 4 years. Disease recurrence was observed in 5 patients (29.4%).

While two patients refused treatment, two were not treated due to advanced age and comorbid diseases. While nine patients were treated with chemoimmunotherapy (8 of 9 patients had R-CHOP and 1 patient had R-CVP treatment), two patients with RT, one patient with chemoimmunotherapy (R-CHOP treatment) and RT, and 1 patient with anti-biotherapy (doxycycline) treatment. In one patient with a mass on the eyelid, the mass was removed by surgical excision, and the eyelid anatomy was reconstructed. In one patient with severe proptosis, exposure to keratitis resulted in a subsequent corneal abscess that extended from the endothelium to the anterior chamber. Aggressive treat-

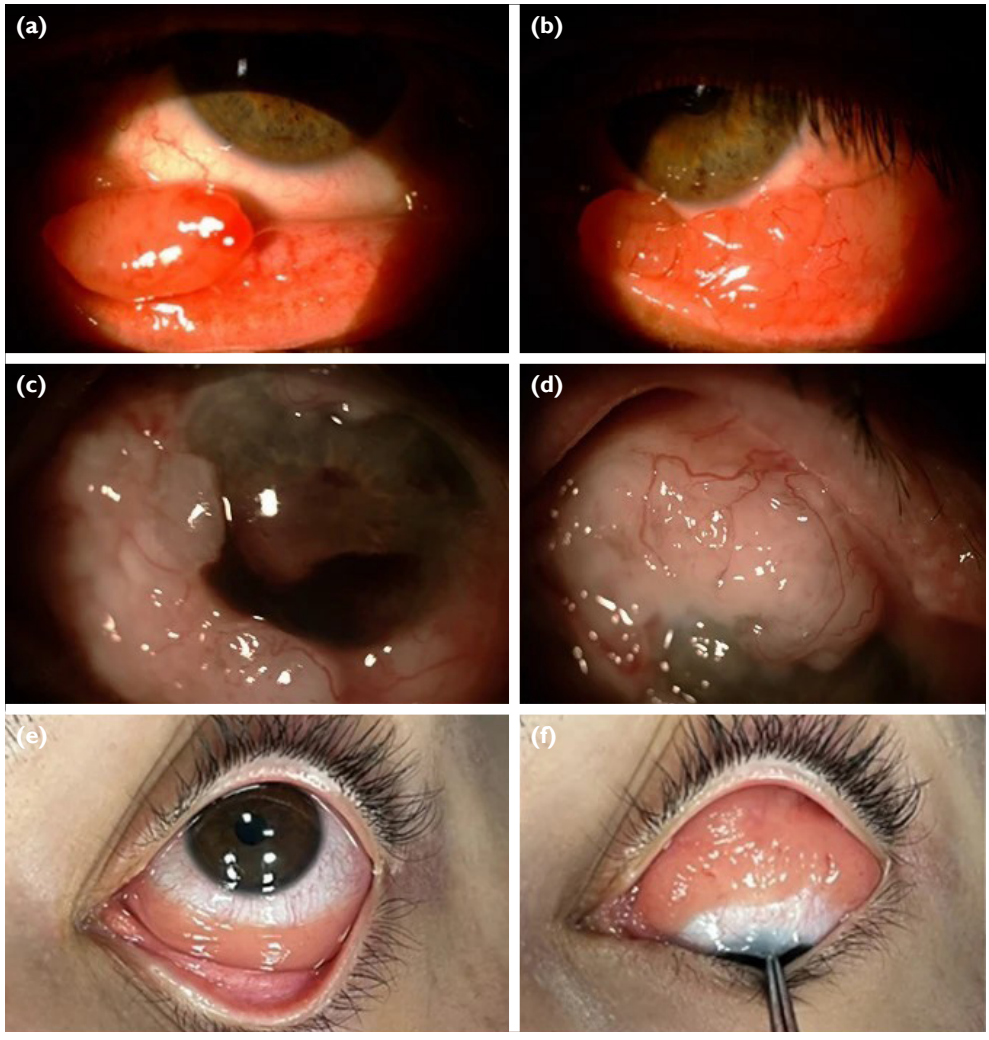

Figure 2. Sample of conjunctival lymphoma cases. **(a, b)** Giant papilla-like multinodular sessile and pedicled lesions on both eyes' lower lid tarsal conjunctiva. **(c, d)** A conjunctival mass extending to approximately 270 degrees in the right eye also invaded the cornea. **(e, f)** Fornicial and epibulbar lymphomas.

ment, including temporary tarsorrhaphy, topical fortified vancomycin and ceftazidime eyedrops every hour, cyclopentolate eyedrop tid, and systemic amoxicillin/clavulanic acid 2×1000 mg (PO), led to the resolution of exposure keratitis. No recurrence was observed in the follow-ups. During the follow-up period, 15 patients were alive, while two died due to non-lymphoma causes.

Thirteen individuals had excellent visual acuities both before and after treatment. In one patient, visual acuity increased from 0.2 to 0.8 with the improvement of ptosis and hypoglobus after treatment. In one patient, visual acuity was 0.2 before and after treatment due to nuclear sclerosis and posterior subcapsular cataracts. Post-treatment visual acuities were light perception negative in one patient with exposure keratitis and another with mature cataract, whose posterior segments could not be visualized.

Discussion

Orbital lymphoma is a painless, slowly progressive unilateral clinical entity. Although orbital lymphoma is mostly seen as primary, the literature shows systemic involvement may be present in 75% of patients. For this reason, even if systemic involvement is not noted at the beginning, systemic screening of these patients should be performed at regular intervals (11,12). Orbit, oral cavity, and oropharynx should be examined in addition to the systemic examination.

Although the incidence of orbital lymphoma increases with age, it is most frequently seen between the 5th and 7th decades (13). Lymphoma is the most common orbital malignancy in adults and may present with different clinical presentations. Depending on the location and mass effect, it may present with different clinical presentations, such as proptosis, ptosis, epiphora, and ophthalmoplegia. Clinical

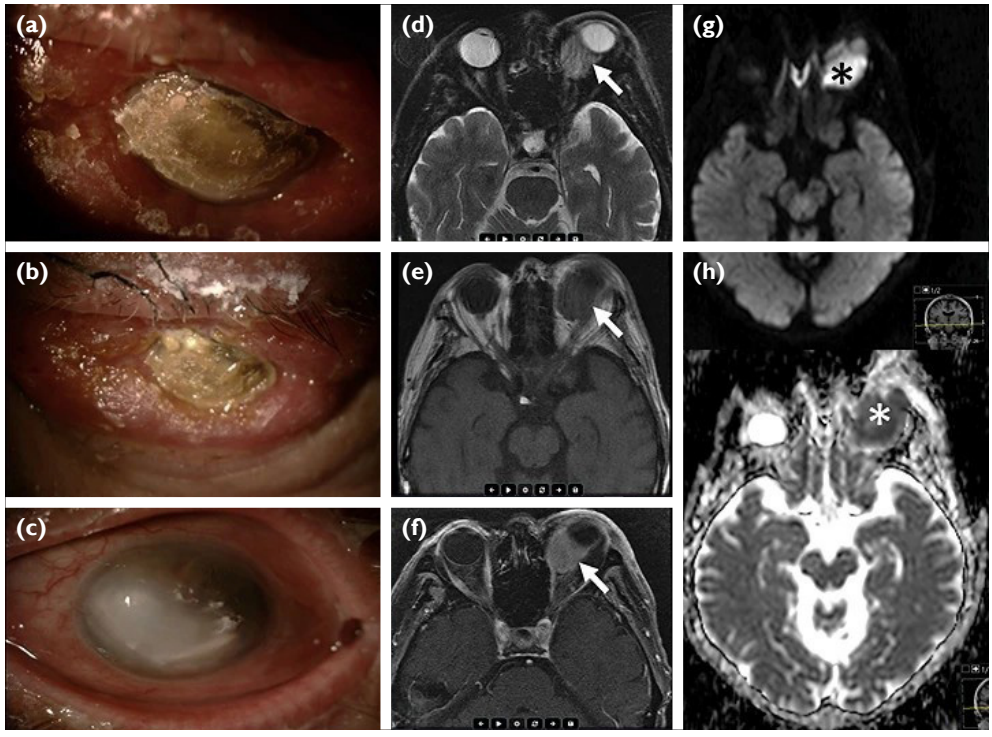

Figure 3. Case with proptosis and exposure keratitis **(a, b)** who improved with treatment **(c)**. Axial T2-weighted **(d)**, T1-weighted **(e)**, and post-contrast fat-suppressed T1-weighted **(f)** images through the orbit show an extraconal mass lesion (arrows). Compared to the gray matter of the brain, the mass is slightly hyperintense on T2 **(d)** and hypointense on T1 **(e)** weighted images, and it shows homogenous and strong contrast enhancement **(f)** after intravenous gadolinium injection. Diffusion-weighted images of the patient. The mass (marked with «an asterisk) is hyperintense in the «trace» image **(g)** and shows low ADC (apparent diffusion coefficient) values on the ADC map **(h)**. Low ADC values are typical of lymphoma.

symptoms play a crucial role in the differential diagnosis of lymphoma. Proptosis and orbital mass are the most prominent clinical presentations (14). Particularly unilateral proptosis or any orbital mass, unexplained epiphora, salmon-pink conjunctival involvement, proptosis, and/or ptosis should arouse clinical suspicion for orbital lymphoma (15-18). The tissues that might be involved, in order of frequency, include the conjunctival, lacrimal, extraocular muscles, and periocular connective tissues (19).

Orbital lymphoma is diagnosed with high clinical suspicion. It is a great imitator of multiple diseases. Late diagnosis might lead to poor visual acuity and life expectancy if orbital lymphoma is not considered in the differential diagnosis of various signs and symptoms. The literature has reported that the clinical symptoms and findings may resemble those of orbital diseases such as dacryocystitis, cavernous hemangioma, orbital meningioma, lacrimal gland epithelial tumor, and Graves' ophthalmopathy (5,20-26). One pediatric patient in our series was worth mentioning in this manner. A 15-year-old patient working in animal husbandry hit an iron stick on his left upper eyelid 1 month ago. The patient was referred for a preliminary diagnosis of pyogenic granuloma due to swelling and redness on the left upper eyelid. His mass continued to progress despite ampicillin-sulbactam treatment. Although lymphoma often involves periorbital involvement, it is atypical that it makes a massive appearance with a hemangiomas appearance and progresses rapidly in one month at the age of 15. The absence of pain and failure to respond to antibiotic treatment should be a warning for other underlying diseases. Local tumors, allergy findings, amyloidosis, and lymphoma should be considered in the differential diagnosis of isolated conjunctival lesions.

In another atypical patient, intraocular lymphoma and orbital lymphoma were seen simultaneously. The patient had intense intraocular vitritis and multiple foci associated with lymphoma in the retina, and a mass was also observed in the conjunctiva. This condition is very rare. This patient had primary aggressive eye lymphoma and central nervous system involvement of orbital lymphoma was observed during follow-up. There have been some reported patients of primary intraocular lymphomas that invade the orbit over time. However, no case of primary orbital lymphomas that have invaded the intraocular tissue has been reported (13). Neudoerfer et al. (27) reported three patients that involved

Table 1. Clinical features of 17 patients with orbital lymphoma

Parameter	Mean±SD (range; median)	Parameter	n (%)
Age	63±19.11 (15–79; 65)	Stage	
Visual acuity at diagnosis	0.76±0.35 (0–1.0; 1)	Stage 1	9 (52.9%)
Visual acuity after treatment	0.75±0.35 (0–1.0; 1)	Stage 2	-
Diagnosis time (months)	7.76±13.99 (1–60; 3)	Stage 3	1 (5.9%)
Follow-up period (months)	76.88±55.77 (1–184; 66)	Stage 4	7 (41.2%)
	n (%)	Diagnosis	
Gender		Marginal zone lymphoma	10 (58.8%)
Male	13 (76.5%)	Diffuse large B-cell lymphoma	5 (29.4%)
Female	4 (23.5%)	Small lymphocytic lymphoma	1 (5.9%)
Involvement		Mature T Cell Lymphoma	1 (5.9%)
Right	7 (41.2%)	Chemotherapy	
Left	9 (52.9%)	Yes	9 (52.9%)
Bilateral	1 (5.9%)	No	8 (47.1%)
Clinical signs and symptoms		Radiotherapy	
Periorbital swelling	5 (29.4%)	Yes	4 (23.5%)
Periorbital swelling+ptosis	3 (17.6%)	No	13 (76.5%)
Periorbital swelling+proptosis+chemosis	1 (5.9%)	Surgical	
Conjunctival mass	6 (35.3%)	Yes	2 (11.8%)
Conjunctival mass+periorbital swelling+hypoglobus	1 (5.9%)	No	15 (88.2%)
		Relapse	
Mass on the Eyelid	1 (5.9%)	Yes	5 (29.4%)
Systemic Involvement		No	11 (64.7%)
Yes	8 (47.1%)	Survival	
No	9 (52.9%)	Yes	15 (88.2%)
		Exitus	2 (11.8%)

SD: Standard deviation.

SLL and presumed systemic lymphoma with simultaneous intraocular and orbital involvement. The biopsy result of our 94-year-old female patient with intraocular and orbital lymphoma was also SLL. A conjunctival mass extending to approximately 270° in the right eye also invaded the cornea. This patient was not treated due to advanced age and co-morbid diseases.

In approximately 80% of ocular adnexal lymphomas (OAL), Chlamydia psittaci DNA has been demonstrated, and doxycycline has been tried to treat these patients. The role of antibiotics against OAL has not been proven due to the lack of objective assessment methods, the unclassification of response rates based on histological subtypes of OAL, and short follow-up. Ferreri et al. (28) reported that the disease regressed in approximately 50% of the patients with eradication treatment in a multicenter, prospective study of ocular adnexal lymphoma patients.

According to the REAL classification, lymphomas are histopathologically classified as low, high, and very high grades. Orbital and adnexal lymphomas are usually low-grade, B-cell-derived, and non-Hodgkin lymphomas. DLBCL is most common after mucosa-associated lymphoid tissue lymphoma (MALToma) (14,29).

Radiologic imaging tools useful in diagnosis and follow-up include CT, MRI, and PET. As seen in our patients, the masses may occupy intraconal or extraconal spaces. Extraconal locations were more frequent in our series. Orbital lymphomatous tissues tend to expand with an infiltrative nature, which results in the molding of preexisting orbital structures such as extraocular muscles, the globe, and the optic nerve. Be-

cause of the tumor's "molding" nature, bone destruction or remodeling is not seen in most patients (20,30). However, bone destruction, foraminal widening, and bone remodeling patients have been reported in some malignant lymphoma subtypes, such as DLBCL and mantle cell lymphoma (20). We have not observed any bone erosions or remodeling.

The tumors were homogenous on CT and MRI in our series, as noted in previous studies (20,30-32). The tumors tend to have a high density similar to the brain cortex on CT and show moderate and homogenous contrast enhancement (30), which was the case in our 10 patients. A previous study found that contrast medium was washed out faster in lymphoma on dynamic CT imaging compared to orbital pseudotumor (33). On MRI, the lymphoma tissues tend to be relatively dark T2 and have an intermediate intensity similar to that of muscles on T1W images. The tissue mostly shows marked or moderate enhancement after gadolinium injection (34). Our findings were consistent with these findings. Diffusion-weighted MRI is also useful in diagnosing lymphoma in the orbit or other locations. Typically, lymphoma is seen as a hyperintense mass on trace DWI images and has low ADC values. Many studies reported lower ADC values for lymphoma, which help differentiate it from other malignant tumors (35). Our patients had low ADC values similar to white matter ADC values. CT and MRI were useful in the follow-up period for the present series.

Seven of our patients had PET scanning and showed increased FDG activity in the orbital mass. PET detects FDG accumulation in tissues. Increased FDG accumulation reflects high glycolytic activity within the cells, which is typical of malignant tissues. That is why PET is a useful tool to scan the whole body to detect cancerous tissues and is used to map the local and far-reaching extension of the primary malignant disease (30).

The treatment strategies for orbital lymphoma vary depending on factors like histological type, disease stage, and individual patient-specific factors. Lymphoma treatment may include RT, chemotherapy, immunomodulating therapy, primary antibiotic treatment, surgical excision, or combination therapy. Surgical excision alone has no place, except for biopsy, due to the high local relapse rates with surgical treatment alone. In the literature, as low-grade primary orbital and OAL, such as MALToma, are mostly confined to the periocular tissue, orbital RT has been mostly elected as a primary treatment (36-41). The target is generally the entire orbit (19). The dose to be used is generally recommended as 24–36 Gy in low-grade OAL and 30–40 Gy in high-grade OAL. It should be remembered that RT -related dermatitis, conjunctivitis, corneal ulcers, xerophthalmia, retinal complications, and cataract formation may develop (42). While RT and chemotherapy combinations effectively prevent recurrence and provide local control in MALToma, good results have been reported with chemotherapy/immunotherapy (Rituximab- an anti-CD20 monoclonal antibody) in DLBCL (14,43). For DLBCL, RT can be used for patients unfit for chemotherapy or with residual disease after chemotherapy (35).

Alfaar et al. (44) showed that conjunctival lymphoma survival rates can be as high as 100%. Hsu et al. (45) showed that 59.8% of the patients responded to first-line treatments, while refractory disease was found in 8.7% of the patients. The lymphoma-related mortality rate was 9.8%. In a study conducted by Akyıldız et al. (46) in Türkiye, patients who responded to first-line treatments were found to be 91.7%. Refractory disease was found in 2.1% of the patients. In our study, 13 patients were treated, and all were alive. One of 13 patients (7.6%) was refractory to first-line treatment. Four of 13 patients (30.6%) relapsed after first-line therapy. Because we have limited and heterogeneous patients, our results may differ from those of other studies.

The main prognostic criteria for OAL were reported as the anatomical location of the tumor, the initial stage of the disease, the subtype of the lymphoma, the immunohistochemical markers that determine factors such as tumor growth rate, and the serum lactate dehydrogenase level (47,48). Ahmed et al. (49) have shown that advanced age, male gender, and diffuse large cell lymphoma are associated with a poor prognosis for orbital lymphoma.

Limitations of this study include a low number of patients with a shorter duration of follow-up period compared to other patients and each of the different histological types of orbital lymphomas in the study. The retrospective nature of the study implies the potential for data gaps. However, as a tertiary university hospital with hematology and oncology departments but no ocular oncology service, this number of patients over 15 years reflects the rarity of the condition.

This is the first study in the literature to present radiological volume measurements of orbital lymphomas. In our patients, we observed that as the tumor volume increased, the clinical signs and symptoms became more pronounced in proportion to its size, although we do not have a statistical outcome on this. Therefore, tumor volume seems to be a predictor of clinical signs and symptoms, and vice versa. Measuring the tumor volume on radiologic images initially and during follow-up allowed us to closely monitor the tumor size and assess the response to the treatment. We believe that raising awareness of tumor volume measurement in future studies will contribute to understanding the impact of tumor volume on the effectiveness of treatment and ultimate prognosis in these patients. In addition, the study shares the outcomes of orbital lymphomas with different clinical presentations.

Conclusion

For the timely diagnosis of orbital lymphoma, a high level of clinical suspicion at the early stages and early referral for a biopsy are the responsibilities of ophthalmologists. Although the treatment plan and implementation are carried out by hematologists and radiation oncologists, follow-up and management of ocular disease and treatment-related eye complications (such as exposure keratitis and radiation cataracts) are the ophthalmologists' responsibility.

This study was presented as a poster at the 55th National Congress of the Turkish Society of Ophthalmology.

Disclosures

Ethics Committee Approval: This study was approved by the Ethical Committee of Dokuz Eylul University (2022/23–18) and was conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

Peer-review: Externally and internally peer-reviewed.

Conflict of Interest: None declared.

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