Ocular Adnexal Lymphoma: Epidemiology and Clinical Characteristics

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ABSTRACT

The aim of the study is to emphasize the frequency, clinical presentation, histopathologic features and TNM staging for each type of ocular adnexal lymphoma (OAL), and investigating treatment results and prognosis in our region. A retrospective review of 54 patients treated for primary and secondary OAL between Jan 2012 and Jan 2019 was made. Epidemiologic data, clinical characteristics of the tumor and recurrence free survival rates were evaluated. Patients with ocular adnexal lymphoma included 27 (50%) women and 27 (50%) men, with a mean age of 60.38±15.36 (range: 18-93) years at the time of presentation. Mean follow-up time was 40.88±20.75 (range 1-84) months. Histopathological diagnosis was extranodal marginal zone lymphoma in 75.9%, diffuse large B-cell lymphoma in 14.8%, chronic lymphocytic leukemia/small lymphocytic lymphoma in 5.6%, mantle cell lymphoma in 1.9% and follicular cell lymphoma in 1.9% of patients. Among 54 patients with OAL 66.7% had orbital, 22.2% had conjunctival, 5.6% had orbital plus conjunctival, 3.7% had orbital plus conjunctival and choroidal, 1.9% had conjunctival plus choroidal involvement. No recurrences were observed in 87.1% of patients during their follow-up. Our data indicates patient epidemiologic data, TNM staging, most common clinical presentation and location of primary and secondary OALs from a single center.

Keywords: Ocular adnexal lymphoma, Orbital lymphoma, Conjunctival lymphoma, Extranodal marginal zone lymphoma, TNM staging

INTRODUCTION

Ocular adnexal lymphoma (OAL) is a malignant lymphoproliferative disease which arises from orbit, lacrimal gland, conjunctiva, and eyelids. OAL is the most common primary orbital malignancy in adult population which accounts for almost 34% of orbital malignancies.[1] OAL accounts for 1-2% of all lymphomas[2] and 8% of all extranodal lymphomas.[3] OAL is a complex diagnosis which comprise different malignant lymphoid tissue involvement. The ocular adnexa may be a secondary involvement site of lymphomas arising from other sites, ocular involvement is observed almost in 5% of non-Hodgkin lymphoma patients over the course of their disease.[2] Orbit, lacrimal gland, eyelid and conjunctiva are four major sites of OAL.[4] While most cases are of B-cell origin, lymphomas of T-cell or NK/T cell could be encountered. Most OALs have no other systemic associations while vitreoretinal lymphoma is related with central nervous system lymphoma.[5] T-cell and NK/T cell lymphomas are rarely observed in the ocular adnexa.[6-7]

Lymphomas are divided into 2 major categories as Hodgkin and non-Hodgkin lymphoma.[8] Hodgkin lymphoma is seen extremely rare in the ocular adnexa. Histopathologic classification of OAL include non-Hodgkin lymphoma subtypes and classified as; follicular lymphoma (FCL), extranodal marginal zone lymphoma (EMZL) of mucosa associated lymphoid tissue, diffuse large B cell lymphoma (DLBCL), mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

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Most common histologic type of OAL is EMZL with 38-100% ratio in different reports.[9] EMZL is also associated with chronic inflammation due to autoimmune diseases and infections. But relation with Chlamidya psittaci in ocular EMZL remain more unclear than gastrointestinal EMZL.[10] Epidemiologic features can cause differences on etiology and clinical aspect in OAL.

Prognosis depends on clinical grading, histopathologic subtype and appropriate treatment for each anatomic type. While radiotherapy (RT) is preferred for particularly solitary orbital lymphoma, chemotherapy with or without RT mostly is preferred for diffuse and metastatic high grade orbital lymphomas.[7] Treatment approach for conjunctival lymphoma is partly similar. T-cell subtype of OAL is extremely rare and associated with poor prognosis.

We present in this study, clinical and epidemiologic characteristics of OAL in a single ocular oncology clinic. Aim of the study is to emphasize the frequency, clinical presentation, and histopathologic features for each type of OAL and investigating treatment results and prognosis in our region.

PATIENTS and METHODS

Data Collection

The medical records of 54 ocular adnexal lymphoma patients treated in our ocular oncology clinic between Jan 2012 and Jan 2019 were retrospectively analyzed. Patients diagnosed with ocular adnexal lymphoma were included in the study. Patients with primary intraocular lymphoma and lesions involving the skin of eyelids were excluded. The study was conducted according to the tenets of the Declaration of Helsinki and ethical approval was obtained from the institutional ethics committee.

Patient files were retrospectively scanned, and data collection was made. All patients had undergone complete staging work-up at presentation. Data collected included the age at the onset of disease, gender, laterality of disease, clinical manifestation, anatomic location of ocular adnexal lymphoma, tissue type involved, histopathological diagnosis, TNM staging of OAL and type of therapy. For patients who did not have a recent TNM staging in medical records, TNM staging was made according to American Joint Committee on Cancer TNM-based staging system[4,11] by the same clinician. Clinical course of disease was interpreted, any complications occurred during follow-up or treatment period were recorded. Presence of systemic lymphoma, recurrence, metastasis or death were recorded.

All patients had a histopathologically proven diagnosis of OAL. Histopathological diagnosis of specimens included EZML, DLBCL, CLL/ SLL, FCL and MCL.

Tissues involved were classified as orbit, conjunctiva, and choroid. Patients with multiple sites involved were classified as conjunctiva plus orbit, choroid plus conjunctiva, conjunctiva plus orbit and choroid.

Initial symptoms at the time of presentation were recorded. Presence of proptosis, ptosis, diplopia, conjunctival hyperemia, ocular pain, decreased visual acuity at the time of onset were noted.

Patients had received external beam radiotherapy, systemic chemotherapy or a combination of these depending on the initial diagnosis and response of tumor to the treatment. Type of treatment was noted for each type of lymphoma. Presence of recurrence, metastasis and death were interpreted at the end of follow-up period.

Ethical Approval was approved by Cerrahpasa Faculty of Medicine Clinical Research Ethical Committee (09/07/2020-86676).

Statistical Analysis

Descriptive statistics were expressed as mean and standard deviation (SD) in normally distributed quantitative data. Normal distribution was evaluated with Shapiro Wilk test. SPSS (version: 21.0) was used for the statistical analysis.

RESULTS

A total of 54 patients were included in the study. Patients with ocular adnexal lymphoma included 27 (50%) women and 27 (50%) men, with a mean age of 60.38±15.36 (range 18-93) years at the time

Table 1. Histopathological diagnosis of OAL and its frequency among groups

	Frequency n (%)	Primary/Secondary OAL	Female / Male
Extranodal marginal zone lymphoma	41 (75.9)	37/4	22/19
Diffuse large B cell lymphoma	8 (14.8)	5/3	2/6
Mantle cell lymphoma	1 (1.9)	1/0	0/1
Follicular cell lymphoma	1 (1.9)	0/1	1/0
CLL/SLL	3 (5.6)	0/3	2/1
Total	54	43/11	27/27

Table 2. TNM staging of primary OALs

TNM stage	Number of patients (%)
T1a	4 (7.4%)
T1b	7 (13%)
T1c	1 (1.9%)
T2a	14 (25.9%)
T2aN1	1 (1.9%)
T2b	13 (24.1%)
T3c	3 (5.6%)
Total	43 (100%)

Table 3. Tissue types involved

Tissue type	Number (%)
Orbit	36 (66.7)
Conjunctiva	12 (22.2)
Conjunctiva+choroid+orbit	2 (3.7)
Orbit+conjunctiva	3 (5.6)
Conjunctiva+choroid	1 (1.9)

of presentation. The mean age for women and men patients were 56.77±17.20 and 64.0± 12.57, respectively.

Mean follow-up time was 40.88±20.75 (range 1-84) months. Eleven (20.4%) patients had bilateral and 43 (79.6%) had unilateral involvement. In patients with unilateral disease 23 (53.48%) had the right eye and 20 (46.51%) had the left eye involved.

One patient diagnosed with diffuse large B-cell lymphoma, had a history of asbestos exposure.

Histopathological Diagnosis and Tissues Involved: Forty-three (79.6%) patients had primary OAL, whereas 11 (20.4%) patients had ocular involvement of systemic lymphoma. All patients had incisional or excisional biopsy for histopathological verification of OAL prior to treatment. Pathological diagnosis information was obtained from patient files. Fourty one (75.9%) patients had EZML, 8 (14.8%) patients were diagnosed with DLBCL, 1 (1.9%) had MCL, 1 (1.9%) had FCL and 3 (5.6%) had CLL/SLL diagnosis (Table 1). Three patients had orbital involvement of chronic lymphocytic leukemia. Three of 4 patients diagnosed with systemic Non-Hodgkin lymphoma had orbital and 1 patient had conjunctival involvement. 1 patient had orbital involvement due to central nervous system diffuse large B cell lymphoma and 1 patient had orbital involvement of splenic marginal zone lymphoma. 2 patients had orbital invasion of maxillary sinus diffuse large B cell lymphoma (Table 1).

The TNM staging of primary OALs is given in Table 2. Among 54 patients with OAL 36 (66.7%) had orbital, 12 (22.2%) had conjunctival, 2 (3.7%) had orbital plus conjunctival and choroidal, 3 (5.6%) had orbital plus conjunctival, 1(1.9%) had conjunctival plus choroidal involvement. Tissue types involved are shown in Table 3 and 5.

Table 4. Frequency of symptoms at presentation

Symptoms at presentation	Frequency n (%)
Mass lesion of the eyelid	24 (44.4%)
Proptosis	19 (35.1%)
Redness	12 (22.2%)
Dyplopia	5 (9.2%)
Ptosis	3 (5.5%)
Decreased visual acuity	2 (3.7%)
Ocular pain	1 (1.8%)

Table 5. Crosstabulation of lymphoma subtype and tissues involved

	Orbit	Conjunctiva	Orbit+Choroid+ Conjunctiva	Orbit+ Conjunctiva	Conjunctiva+ Choroid	Total
Subtype						
EZML	23	12	2	3	1	41
DLBCL	8	0	0	0	0	8
MCL	1	0	0	0	0	1
FCL	1	0	0	0	0	1
CLL/SLL	3	0	0	0	0	3
Total	36	12	2	3	1	54

Symptoms: The most common symptoms at presentation were eyelid tumor, proptosis, and hyperemia, respectively. Patients also reported ptosis, diplopia, decreased visual acuity, redness and ocular pain. Table 4 shows the prevalence of symptoms at presentation.

Treatment, complications, and outcome: Patients were treated according to disease extent and histopathological subtype. Thirty patients received EBRT and 5 patients received a combination of EBRT and chemotherapy. Seven patients received chemotherapy, solely. Chemotherapy regimen consisted of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), rituximab was added to standard chemotherapy regimen in 2 patients. Total excision was performed in 9 patients, local rituximab was given as an adjuvant therapy in 3 of these patients. 3 patients were observed without treatment after incisional diagnostic biopsy (Table 6).

Recurrences were observed in 7 patients (12.9%) after initial treatment. Histopathological diagnosis were EZML in 3 patients, DLBCL in 3 patients and CLL/SLL in 1 patient. In 2 patients who were diagnosed with EZML recurrences were treated with additional radiotherapy and 1 patient was treated with local cryotherapy. Recurrences in 2 patients with DLBCL which were secondary OALs, were treated with chemotherapy. One patient with recurrent primary DLBCL was treated with radiotherapy. The patient diagnosed with CLL/SLL received additional chemotherapy for the treatment of recurrence (Table 7).

Table 6. Treatment modalities and follow-up period according to histopathologic subtypes

	EZML n/(%)	DLBCL n/(%)	MCL n/(%)	FCL n/(%)	CLL/SLL n/(%)
EBRT	26 (48.1)	4 (7.4)	-	-	-
EBRT+CT	1 (1.8)	3 (5.5)	-	-	1 (1.9)
CT	4 (7.4)	0	-	1 (1.9)	2 (3.8)
Total excision	4 (7.4)	1 (1.9)	1 (1.9)	-	-
Total excision+Rtx	3 (5.5)	0	-	-	-
Observation	3 (5.5)	0	-	-	-
Total	41 (75.9)	8 (14.8)	1 (1.9)	1 (1.9)	3 (5.5)
	EZML	**DLBCL**	**MCL**	**FCL**	**CLL/SLL**
Mean follow-up time (range)	41.85±21.38 (1-84)	36.13±22.64 (3-60)	48	60	32.0±6.92 (24-36)

EBRT: external beam radiotherapy, CT: chemotherapy, Rtx: rituximab (administered locally), N: number

Table 7. Treatments applied for recurrences and follow-up period for each histopathologic subtype

	EZML (follow-up period for each patient)	DLBCL (follow-up period for each patient)	CLL/SLL (follow-up period for each patient)
Radiotherapy	2 (51, 60 months)	1 (24 months)	–
Criyotherapy	1 (49 months)	–	–
Chemotherapy	–	2 (6, 40 months)	1 (36 months)
Total	3	3	1

One patient who received EBRT for bilateral conjunctival marginal zone lymphoma developed radiation retinopathy which was treated with intravitreal anti-VEGF.

Distant metastasis or death due to uncontrolled tumor were not observed in any of the patients during the entire follow-up period. Only 2 patients with EZML passed away as a result of other health conditions.

DISCUSSION

The present study group consisted of 54 patients with B-cell origin OALs from a single center. Patients were mostly of advanced age with equal gender distribution. The median age reported in previous studies were between 64 and 70 years.[12-16] The overall mean age was 60.38±15.36 years in our study, which confirms the previous studies. The mean age at presentation was slightly lower in women compared to men (56.77±17.20 versus 64±12.57). Both genders were equally affected in our study as in previous studies.[13-17]

Patients may present with various symptoms depending on the location of the lesion. The most common symptom in our series was mass lesion of the eyelid followed by proptosis and redness. Ptosis, diplopia, decreased visual acuity and ocular pain were less common.

Previously, bilateral involvement in patients with ophthalmic and intraocular non-Hodgkin lymphoma was reported between 10% and 20%.[7,12,16] Bilaterality in our case series was 20.4%. Distribution of histopathological subtypes among case series is the possible reason for this difference.

Meunier et al. reported that, the most common sites involved were the orbit (50%) and conjunctiva (38%).[12] In our case series, we observed that the most common site of involvement was the orbit followed by conjunctiva with a rate of 66.7% and 22.2%, respectively.

The most common B cell lymphoma is reported to be EZML followed by DLBCL or FCL.[14,18,19] A review by Olsen et al. in 2019, reported a total case of 2,211 of orbital lymphoma. In this review the most common B-cell lymphoma was reported to be EZML (59%), followed by DLBCL (23%), FCL (9%) and MCL (5%) respectively.[7] In our study the most common OAL was EZML with rate of 75.9% followed by DLBCL with a rate of 14.8%. The data is consistent with the literature with a relatively higher rate of EZML compared to other studies. The higher rate of EZML is possibly due to relatively small number of study group.

Primary OALs are limited to ocular adnexa and have no evidence of concurrent or prior history of systemic involvement whereas secondary OALs have a biopsy proven prior history or concurrent diagnosis of a systemic disease.[7] The frequency of primary and secondary OAL is reported as 73% and 27% respectively.[7] Our data is consistent with previous studies, with a ratio of 79.6% and 20.3% for primary and secondary lymphoma, respectively. Two patients diagnosed with secondary DLBCL had direct local invasion of the orbit from maxillary sinus. All ocular adnexal CLL/SLL patients had secondary disease. A large percentage of DLBCL (37.5%) were secondary, whereas EZML (10.8%) was often observed as a primary lymphoma.

Two cases of secondary splenic marginal zone lymphoma of the orbit were described previously.[14] The patient with secondary splenic marginal zone

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	EZML (follow-up period for each patient)	DLBCL (follow-up period for each patient)	CLL/SLL (follow-up period for each patient)
Radiotherapy	2 (51, 60 mo)	1 (24 mo)	-
Criyotherapy	1 (49 mo)	-	-
Chemotherapy	-	2 (6, 40 mo)	1 (36 mo)
Total	3	3	1

lymphoma was a 75-year-old female in our study. The patient had a history of splenectomy and a pathologically verified diagnosis of splenic marginal zone lymphoma 10 months before the presentation of the orbital disease. The ocular adnexal lesion was located in the superior orbit and was treated with EBRT, no recurrences were observed during the 46 months follow-up period.

Patient tailored treatment constitutes importance in the management of OALs. Each OAL is treated depending on the special features of tumor.[20] EZML is an indolent form of lymphoma and the primary treatment for EZML consists of EBRT.[21-23] In our study majority of patients (48.1%) with EZML also received EBRT solely. According to the characteristics of tumor, the patients were treated with a variable spectrum from follow-up alone after diagnostic biopsy to chemotherapy combined with EBRT. DLBCL requires a more intense therapy. EBRT alone or in combination with chemotherapy was the preferred type of treatments for DLBCL in our study.

Recurrence free survival was reported between 64% and 85% in previous studies.[12,13,24] In our study, no recurrences were observed in 87.1% of patients during their follow-up. The overall recurrence rate was 12.9% among all the histopathological subtypes. Recurrences were more common in patients with DLBCL compared to other subtypes. Recurrence rates were 37.5%, 33.3% and 7.3% for DLBCL, CLL/SLL and EZML, respectively. Recurrences commonly occurred in stage T4 and T2 patients in our study (2 patients had stage T4 and 4 patients had stage T2 OAL), only 1 patient had stage T1 OAL. Recurrences were treated depending on the disease characteristics. Recurrences of EZML were treated with radiotherapy or local criyotherapy, whereas chemotherapy was applied for the recurrences of DLBCL and CLL/SLL.

The limitations of the present study include relatively short period of follow-up. Due to the nature of disease course, OALs differ in histopathological subtypes and disease extent which causes a disparity among patient group. Treatment options also differ according to patient and disease specifics.

In conclusion, considering the rarity of OAL, our study included a relatively large number of patients in a single center with a mean follow-up period of 40 months. Our study confirmed the fundamental characteristics of OAL's as reported in the literature.

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