Ocular Adnexal Lymphomas: An Eye Care Service Experience in Turkey

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Aim: This study aimed to evaluate the clinical and pathological features of ocular adnexal lymphoma (OAL) and the treatment results in an eye care service center in Turkey.

Materials and Methods: The data sets of the patients diagnosed with OAL acquired between January 2008 and January 2016 were collected and analyzed.

Results: Fifteen patients were included in our study. The mean age was 55.80 ± 17.85 years. The age range was 7–85 years. Most of the lesions originated from orbital tissue, and histopathological and immunohistochemistry examinations of the lesions were consistent with non-Hodgkin’s lymphoma in 14 patients and Hodgkin’s lymphoma in 1 patient. The most common subtype of OAL, accounting for 40% of cases, is extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type.

Conclusion: Most of our patients’ histopathological and immunohistochemistry examinations are non-Hodgkin’s type and also involve the orbits. Ocular adnexal lymphomatosis is not a rare disorder and could be treated if there is no systemic involvement at first diagnosis.

Keywords: Adnexal Lymphoma, Non-Hodgkin’s lymphoma, tumour

INTRODUCTION

Lymphoid tumors are the most common primary orbital malignancy in adults.[1] Lymphomas of the ocular adnexa are a heterogeneous group of malignancies, accounting for approximately 1%–2% of non-Hodgkin’s lymphomas (NHLs) and 8% of extranodal lymphomas.[1] According to surveillance, epidemiology, and end results’ data, the incidence of ocular adnexal lymphoma (OAL) has risen steadily between 1975 and 2001, with an annual increase of 6.3%. [2] As a disease entity, it was first described in 1983 by Isaacson and Wright[3] and it is now well established in the Revised European-American Lymphoma classification of lymphoid neoplasms and the more recently published World Health Organization (WHO) classification system.[1]

The aim of this study was to evaluate the clinical and pathological features and the treatment outcome in patients who were diagnosed with OAL in our clinic.

MATERIALS AND METHODS

Fifteen patients diagnosed with OAL between January 2008 and January 2016 were included in this study. The hospital’s ethics committee approved this study. The records of these patients were examined retrospectively. Patients diagnosed with lymphoma were included in the study if their histopathological diagnosis was proved by orbital or periocular biopsy. Systemic lymphoma patients with optic nerve involvement or intraocular lymphoma were excluded from this study. The localization, unilaterality or bilaterality, and the clinical grade of the tumor as at the time of diagnosis, age, gender, the visual acuity before and after the treatment, and anterior and posterior segment examination findings of the patients were evaluated. The localization of the tumor was detected by clinical and radiological methods such as computed tomography (CT) and magnetic resonance imaging (MRI). The incisional biopsy/subtotal excision was usually performed for the diagnosis of lymphoma in the patients.

The total excision was performed if it was possible to extract the whole tumor. The diagnosis of lymphoma was...
made on the basis of morphologic, immunophenotypic, molecular, and cytogenetic evaluations of tissue biopsy specimen. The term extranodal involvement indicates either primary involvement or a manifestation of extensively disseminated systemic disease. Investigations such as whole blood count, peripheral smear, thorax, and abdominal CT, and bone marrow and lymph node biopsies were performed in patients who had no evidence of systemic disease after previous evaluation by an hematologist and an oncologist. Ann Arbor classification was used for staging of lymphoma. The patients had systemic examination at 6-month interval after the treatment if there was no evidence of systemic lymphoma as at the time of diagnosis. The patients were informed about the disease and its course. The treatment modality was planned according to the systemic involvement of the disease by the hematologist and a radio-Oncologist.

External radiotherapy was performed after the surgery if the involvement was limited to the peri orbital area; however, chemotherapy was planned if there was systemic involvement of the lymphoma.

The selection of treatment for OAL was dependent on the specific tumor type and its staging. Aggressive lymphoma such as diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) or low-grade lymphoma such as extranodal marginal zone lymphoma (EMZL) with symptomatic systemic involvement had the R-CHOP intravenous cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² (maximum dose 2 mg), and rituximab 375 mg/m² on day 1, and oral prednisolone 40 mg/m² on days 1–5, administered every 21 days for a total of six or eight cycles were applied in the systemic chemotherapy treatment. R-CODOX-M was intravenous cyclophosphamide 800 mg/m² on day 1 and 200 mg/m² on days 2–5, doxorubicin 40 mg/m² on day 1, vincristine 1.5 mg/m² (maximum dose 2 mg) on days 1, 8, and 15, methotrexate 3 g/m² in over 24 h on day 8 and rituximab 375 mg/m² on day 1, intrathecal cytarabine 70 mg on days 1 and 3 with intrathecal methotrexate 12mg on day 15, alternating with R-IVAC was intravenous rituximab 375 mg/m² on day 1, ifosfamide mixed with mesna 1800 mg/m² on days 1–5, cytarabine 2 g/m² on days 1 and 2, etoposide 60 mg/m² on days 1–5, and intrathecal methotrexate 12 mg on day 5 were applied in the systemic chemotherapy treatment protocol was applied in Burkitt lymphoma (BL). In some cases with low-grade lymphoma, observation without intervention is selected. ABVD (combined modality consisting of intravenous doxorubicin 25 mg/m², bleomycin 10 units/m², vinblastine 6 mg/m², and dacarbazine 375 mg/m² on days 1 and 15; every 28 days generally for four to six cycles) was applied in Hodgkin’s lymphoma.

**Results**

The study evaluated 15 eyes of 14 OAL patient datasets. The mean age of the patients with OAL was 55.80 ± 17.85 years. Age range was 7–85 years. Of the patients, 7 (47%) were female and 8 (53%) were male. The right eye was affected in 5 patients (33%), left eye in 9 (67%) patients, and bilateral involvement was in 1 patient. The involvement of the orbit, eye lid, conjunctiva, lacrimal gland, lacrimal sac, paranasal sinus was, respectively, in 6, 4, 3, 1, 1, and 1 of the patients. There was also involvement of lacrimal gland, orbit, and eye lid altogether in one patient. There was eye lid edema, especially obvious at superolateral side of the orbit, in patients who have lacrimal gland involvement, and ptosis and medial shift of the globe in the other patients. The common signs in patients who have orbital involvement were the presence of a hard mass, restriction of ocular motility, proptosis, exophthalmos, squint, and ptosis. Radiological investigations including CT and MRI were done to determine the location, size, and the depth of the infiltration of the lesion. There was an irregularly appearing mass that was hypo-isointense on T1-weighted images or iso-hyperintense on T2-weighted images on MRI at most of the patients. There was contrast matter retention after gadolinium injection.

Total excision was done in 6 (40%), subtotal excision in 5 (33%), and incisional biopsy in 4 (27%) patients. Histopathological properties include non-Hodgkin’s lymphoma in 14 patients (93%) and Hodgkin’s lymphoma in one patient (7%). The histopathological and immunophenotypic distributions of the NHL patients according to the WHO classification system were as follows: extranodal marginal zone (EMZL, mucosa-associated lymphoid tissue [MALT] lymphoma) in six patients, small lymphocytic lymphoma (SLL) in one patient, DLBCL in three patients, MCL in two patients, follicular lymphoma (FL) in one patient, and BL in one patient. The subtype of Hodgkin’s lymphoma was nodular sclerosis.

Eight patients were in control previously at an hematology-oncology clinic because of systemic lymphoma whereas there was no evidence of systemic lymphoma in seven patients. Systemic lymphoma signs developed in one patient (15%) during follow-up.

External radiotherapy was administered to six (42.8%) patients. Orbital radiotherapy was administered as 25–40 Gy dose in these patients. Chemotherapy was administered to eight patients because of the extraocular systemic involvement. One patient had chemotherapy
Because of detection of systemic involvement after radiotherapy.

Keratopathy and dry eye syndrome were seen in three patients after an average of 42.8 ± 19.6 (range: 18–96 months) months’ follow-up. There was no mortality in our patients that were under control.

**Discussion**

Lymphomas constitute the most frequent malignant tumors of the ocular adnexa; in the Florida Cancer Registry, they represent up to 55% of all orbital tumors. The majority of OAL are primary extranodal neoplasms; however, 10%–32% are secondary tumors in patients with disseminated lymphoma. More than 95% are of B-cell origin and 80% are low-grade lymphomas. The most common subtype of primary OAL, accounting for 35%–80% of cases, is extranodal marginal zone lymphoma (ENMZL) of MALT type followed by FL (20%), DLBCL (8%), and less commonly MCL, SLL, and lymphoplasmacytic lymphoma. Few cases of primary T-cell lymphoma and Hodkin’s lymphoma of the ocular adnexa have been reported.

In Japan and Korea, the proportion of MALT lymphoma among primary OAL appears to be higher (80%–90%) than that in Western countries. Secondary ocular involvement occurs in 2.4%–5.3% of patients with advanced systemic NHL. Of note, ENMZL with secondary ocular manifestation typically involves simultaneously other extranodal MALT sites.

OAL is seen in all ages but especially peaks between 50 and 70 years. It is also more common in females than males. The average age in the studies that were done in our country was reported as 56 years by Pazarlı et al., 54.6 years by Soysal et al., and 61.6 years by Çalış et al. The average age in our study was 55.8 years which is similar to other studies, whereas male-to-female ratio was found to be almost the same (8/7).

Even if OAL is generally seen unilaterally, bilateral involvement is also encountered. In addition, there was one patient (6.7%) with bilateral lymphoma in our study. Most researchers reported orbital involvement in lymphoma more than other adnexal structures. There was involvement of the orbit in 9 patients (60%), eye lid in 4 (26.7%) patients, parasenal sinus in 1 patient (6.7%), and lacrimal sac in 1 (6.7%) patient. Like previous studies in our country, orbital involvement was predominant.

A lot is still unknown about the clinical manifestation, histopathology, and prognosis of OAL.

There are many studies about primary orbital lymphomas without any systemic signs or symptoms in the literature.

There could be some difficulties in the differentiation of the primary or secondary orbital lymphomas in some patients. Orbit and adnexa are the only sites for extranodal involvement of the primary OAL and the disease is restricted to that site. These are accepted as Stage IE in Ann Arbor classification.

Orbital signs could be seen simultaneously with the systemic involvement or later in secondary OAL. Lymphatic involvement in other parts of the body has been demonstrated in patients with OAL with the new developments in diagnostic methods such as positron emission tomography (PET), bone marrow biopsy, and gastrointestinal endoscopy.

Due to this, it was claimed that the prevalence of the primary lymphomas could be lesser than that of the previous reports. High systemic involvement ratios, i.e., 75% by Pazarlı et al. and 62% by Soysal et al., were reported in OAL. Systemic involvement after an average 3.5-year follow-up was detected as 60% in our study. Due to this reason, even if there is no systemic involvement at the first diagnosis, long-term follow-up and systemic scanning should be done regularly, especially in patients with orbital disease.

OALs are mostly seen as non-Hodgkin’s type but rarely Hodgkin’s lymphomas could also involve the orbit. Extranodal involvement was mostly in the type of NHL in the studies that were reported in our country. NHL was seen in 14 patients and Hodkin’s lymphoma in 1 patient in our study. Low-grade groups were mostly seen in non-Hodgkin’s type in the patients who had OAL diagnosis according to the reports in the literature. Most of the patients were in the type of MALT lymphoma that was one of the low-grade lymphomas and second in the type of diffuse large B-cell lymphoma in our study. There were similar results in the studies that were done by Soysal et al. and Çalış et al. in our country.

The decision of the treatment of the patients who had the diagnosis of OAL should be made after the systemic examination. PET-CT is used to detect systemic involvement. Chemotherapy or combined chemotherapy and orbital radiotherapy should be preferred after detecting systemic involvement.

External radiotherapy is 97% effective in periocular lymphomas to control localized tumor. The preferred dose usually should be 24–36 Gy in low-grade OAL and 30–40 Gy in high-grade OAL. External radiotherapy was used (54%) in the treatment of OAL in our clinic and no recurrence was detected in the follow-up period. Systemic involvement was developed in one patient. Keratopathy and dry eye syndrome were the complications usually seen as side effects.
Combined chemotherapy and radiotherapy was compared in Stage 1E lymphoma patients in a clinical study.[31] There was no difference between the two groups after evaluating the long-term results. It was reported that radiotherapy could be chosen as a first choice in the treatment of periocular lesions.

R-CHOP was often preferred in the chemotherapy regimens that are used in systemic involvement. Therapy regimen is administered as six cures with 3-week intervals. Hematological side effects such as neutropenia, anemia, thrombocytopenia related to chemotherapy, and side effects because of drug toxicity could be seen.[32,33] R-CHOP protocol was used as a chemotherapy regimen in our four patients with systemic involvement and any recurrence was seen during follow-up.

Ben Simon et al.[34] applied a total of 600 mg dose of oral chlorambucil in four cures as a single treatment agent in advanced-age OAL patients in their study and achieved 79% success rate but detected 12% recurrence rate. Song et al.[35] applied cyclophosphamide, vincristine, and prednisolone protocol as a first treatment modality because of the ophthalmic side effects of the radiotherapy in 21 ocular adnexal EMZL patients in their study and achieved 76.2% complete remission. There had been extraorbital recurrence in two patients and local recurrence in five patients during 58-month follow-up period. 30 Gy radiotherapy was applied to patients with local recurrence.

**CONCLUSION**

As a result, OAL is not a rare disorder and could be seen with different signs and symptoms according to the localization of the tumor. The clinical and radiological signs of the patients should be assessed carefully. Treatment protocol should begin with the histological and immunophenotypic diagnoses following the incision/subtotal>Total excision of the tumor according to its nature and after systemic examination, and the other therapy models should follow this.

Survival and visual prognosis could be satisfactory with appropriate treatment. Even if there is no systemic involvement at the first diagnosis, systemic scanning should be done regularly in every visit and patients should be assessed with multidisciplinary approach. External radiotherapy is the gold standard in periocular lymphomas and systemic chemotherapy is the gold standard in systemic involvement according to the literature.[23,29,36-38]

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

Kiziltas, et al.: Ocular adnexal lymphomas in Turkey


