

Ocular Adnexal Lymphoma: Clinical Presentation, Diagnosis, Treatment and Prognosis

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Abstract

Ocular adnexal lymphoma (OAL) is a rare tumor with an incidence of 0.2 per 1,00,000 individuals. However, it constitutes the most common orbital tumor especially in older population with an incidence ranging from 11% to 24%. OAL can involve conjunctiva, orbital soft tissues, eyelid, or adnexal structures such as lacrimal gland and lacrimal drainage system. The most common primary OAL is low-grade malignant extranodal marginal zone B-cell lymphoma (EMZL) of mucosa-associated lymphoid tissue (MALT) type. Though various classification and staging systems have been proposed for OAL, currently, American joint committee on cancer (AJCC) TNM (tumor node metastasis) staging is most commonly used. Most commonly, conjunctival lymphoma typically presents as 'salmon-colored patch' and orbital lymphoma presents as proptosis, which on imaging shows characteristic appearance of molding around the globe without any globe indentation or bone erosion. Orbital radiotherapy and systemic chemotherapy forms the mainstay of treatment. Newer treatment modalities include immunotherapy with interferon and anti-CD20 antibody rituximab that have been shown to be useful either when used alone or in combination with chemotherapy or as radio-immunotherapy.

Keywords: Eye; Conjunctiva; Orbit; Lymphoma; Ocular adnexal lymphoma; Orbital lymphoproliferative disease

Introduction and Historical Perspectives

Orbital lymphoproliferative disorders or ocular adnexal lymphoma (OAL) comprises of heterogeneous group of lymphoid cell disorders that can involve conjunctiva, orbital soft tissues, eyelid, or adnexal structures such as lacrimal gland and lacrimal drainage system [1]. Broadly, they are classified as Hodgkins and non-Hodgkins lymphoma (NHL). Majority of OAL are low grade B-cell NHL. NHL can arise from precursors or from matured lymphocytes such as B-cells (80%), T-cells (14%) and sometimes from Natural Killer (NK) cells (6%) [2]. These disorders are characterized and classified based on the clinical presentation, histologic features, immunological characteristics, and molecular and genetic composition [1,3]. Many classification systems have been put forward over the past few years with increased understanding of the genetics, cell markers, and pathogenesis of these disorders.

Earlier classifications such as Rappaport classification were based on morphological criteria [4]. It divided NHL as nodular/diffuse and into following types: lymphocytic well-differentiated, lymphocytic poorly-differentiated, mixed cell (lymphocytic and histiocytic), histiocytic, and undifferentiated. Although useful it suffered inappropriate terminology, lacked specific disease entities and clubbed both large B-cell and T-cell lymphomas into a single histiocytic type. Later on, two classification systems were proposed by Lukes-Collins and Klien respectively, based on differentiation into B-cells and T-cells [5,6]. Lukes-Collins classification was used in the United States of America and Klien classification was popular in Europe. At that time no nomenclature system existed to translate one classification to another [7]. In 1982, national cancer institute (NCI) published the working formulation (WF) for clinical usage based on large multicenter study, which involved North America and Europe [8]. WF classified lymphomas based on natural history, survival characteristics but did not classify them into B or T-cells lymphomas. Later on in 1994, international lymphoma study group (ILSG) constituted by hematopathologists developed the REAL (Revised European-American Classification of Lymphoid Neoplasms) classification which was incorporated into WHO classification with

minor modifications [7]. Ann Arbor classification which was given for Hodgkins lymphoma in 1971 was also used for classifying OAL [9]. However, all the above classification systems were described for systemic lymphomas and none of them included ocular/orbital site-specific information. Also differentiation into sub-types for useful clinical information, tumor size, tumor location, predicting outcome and prognosis was lacking in old classification systems. In 2009, in the seventh edition of the American joint committee on cancer (AJCC) staging manual, TNM (tumor node metastasis) staging of OAL was proposed. TNM staging was put forward with the aim of identifying clinical and histologic features of prognostic significance, providing anatomic details and standard nomenclature for multicenter and international collaborations [10].

Epidemiology

International association of cancer registries (IACR) 2014 by WHO, identified NHL as the 5th most common tumor in men and 7th in women in the United states [11]. Ocular and adnexal lymphoma comprises 5% to 10% of all extranodal lymphomas [12]. Incidence of OAL is estimated at 0.2 per 1,00,000 individuals [12]. OAL however is the most common orbital tumor especially in older population with an incidence ranging from 11% to 24% of all the orbital tumors [13,14]. Bilateral disease is observed in about 10% to 15% of cases [1,13]. Incidence of NHL in general population is on the rise [15,16]. Reasons put forward are immunodeficiency syndromes, organ transplantation, autoimmune diseases, and involvement of several pathogenic viruses

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Primary tumor	Definition
T	
Tx	Lymphoma extent not specified
T0	No evidence of lymphoma
T1	Lymphoma involving the conjunctiva alone without orbital involvement
T1a	Bulbar conjunctiva only
T1b	Palpebral conjunctiva +/- fornix +/- caruncle
T1c	Bulbar and nonbulbar conjunctival involvement
T2	
T2a	Anterior orbital involvement but not involving the lacrimal gland (with or without conjunctival involvement)
T2b	Anterior orbital involvement with lacrimal gland involvement (with or without conjunctival involvement)
T2c	Posterior orbital involvement (with or without conjunctival involvement; with or without extraocular muscle involvement)
T2d	Nasolacrimal drainage system involvement (with or without conjunctival involvement; not involving the nasopharynx)
T3	Preseptal eyelid involvement (with or without conjunctival involvement; with or without orbital involvement)
T4	
T4a	Involvement of nasopharynx
T4b	Osseous involvement including periosteum
T4c	Involvement of paranasal sinuses
T4d	Intracranial spread
Lymph node involvement (N)	
Nx	Involvement of lymph nodes not assessed
N0	No evidence of lymph node involvement
N1	Involvement of ipsilateral regional lymph nodes
N2	Involvement of contralateral or bilateral regional lymph nodes
N3	Involvement of peripheral lymph nodes not draining ocular adnexal region
N4	Involvement of central lymph nodes
Distant metastasis (M)	
Mx	Dissemination of lymphoma not assessed
M0	No evidence of involvement of other extranodal sites
M1	Lymphomatous involvement in other organs detected at the time of initial diagnosis or subsequently
M1a	Noncontiguous involvement of tissues or organs external to the ocular adnexa (including parotid gland, submandibular gland, lung, liver, spleen, kidney, breast)
M1b	Lymphomatous involvement of the bone marrow
M1c	Both M1a and M1b

Adapted from: Coupland SE, White VA, Rootman J, Damato B, Finger PT (2009). TNM Staging of Ocular Adnexal Lymphomas. In: Edge SE, Byrd DR, Carducci MA, Compton CA (Eds). AJCC Cancer Staging Manual. (7th edn), Springer, New York, NY, USA.

Table 1: Ocular adnexal lymphoma based on American joint cancer committee (AJCC) classification.

[15,16]. Also more variants are getting diagnosed now because of newer classification systems that have incorporated characteristics other than morphology. There are few studies that have suggested that even the incidence of OAL is increasing [17,18]. The most common primary OAL is low-grade malignant extranodal marginal zone B-cell lymphoma (EMZL) of mucosa-associated lymphoid tissue (MALT) type, while the most common primary intraocular lymphoma is diffuse large B-cell lymphoma (DLBCL) of high-grade malignancy arising from retina [19]. Systemic disease can also involve ocular tissues secondarily, and the most common type of secondary OAL is follicular lymphoma while most common secondary intraocular lymphoma is again DLBCL [19].

Current Terminology, Classification, and Staging

WHO classification aims to define the lymphomas based on both pathological findings and clinical use. Fourth edition of WHO classification is a revised REAL classification initially proposed in 2008 [2,20]. It differed from the 3rd edition in the following ways: inclusion of early neoplastic changes, definition of neoplasm based on age, impact of site and recognition of certain borderline types based on morphology, immunophenotypic and genetic criteria [21].

AJCC 7th edition described the TNM staging of OAL in 2009 (Table 1) [10]. TNM staging includes anatomic site details, better

documentation with more precise description of tumor, provides prognostic significance, treatment outcomes, and can be used as a common nomenclature in international trials [10,22,23]. TNM staging is used for primary OAL only and does not apply to secondary adnexal lymphoma or intraocular lymphomas.

Etiopathogenesis and Immunology

Lymphoma in gastro-intestinal tract is observed to be associated with *Helicobacter pylori* in more than 90% cases [24]. Recently *Helicobacter pylori*, *Chlamydia psittaci*, Hepatitis-C, human Herpes virus, human T-cell lymphotropic virus type-1 (HTLV-1) and Epstein-Barr virus (EBV) have been reported to be associated with OAL [25-27].

Lymphomas arise from lymphocytes during various stages of their development from pre-B cells till maturation into memory B cells. EMZL and lymphoplasmacytic lymphoma (LPL) arise from memory-B cells. Germinal center lymphocytes are thought to give rise to DLBCL (which arises from centroblasts) and follicular lymphoma (which arises from centrocytes) whereas mature naïve B cells give rise to Mantle cell lymphoma [28].

Flow cytometry allows immunophenotype analysis of lymphocytes and helps in understanding the composition as well as diagnosing the

specific OAL type. Table 2 summarizes the immunophenotypes of important OALs [28].

Clinical Features

OAL presents as insidious onset, slowly progressive and painless mass involving eyelid, orbital soft tissue, muscle, lacrimal gland or conjunctival tissues. Age at presentation is commonly between 5th to 7th decades of life [29] and it is the most common orbital tumor (accounting for 24% cases) in age group >60 years [13]. Though some studies show a female preponderance [29], in general, there is no gender predilection [30]. Symptoms may include: proptosis, eyelid mass, conjunctival mass, diplopia, ocular motility restriction but visual compromise is uncommon. Atypical features include pain, inflammation, and rapidly progressing mass with optic nerve compromise [13,19,29].

Conjunctival OAL is typically seen as a salmon color patch either below bulbar or palpebral conjunctiva. This appearance is caused by presence of intrinsic vessels within the lymphoma, abundant cellular tissue and lack of interstitial matrix [31]. Conjunctival lymphoma arises from substantia propria and therefore overlying epithelium is usually normal. It's important to look for superior and inferior fornix involvement. Careful examination is needed to rule out co-existent eyelid or orbital component and vice-versa. Palpation of lacrimal gland should be done to rule out its enlargement (Figures 1 and 2).

Eyelid OAL usually involves upper eyelid and is preseptal in location. These are typically palpable as soft rubbery mass with defined posterior extent. It is important to differentiate these masses from enlarged palpebral or orbital lobe of lacrimal gland and rule out associated orbital/conjunctival lymphoma.

	BIOMED 2	Discovery	Validation
n=	19	37	52
IgL	16%	37.80%	-
2 IGK VJ	58%	81.10%	44.20%
2 IGK KDE	42%	27.00%	23.10%
IGH FR111	42%	32.40%	36.50%
IGK VJ+KDE	68%	83.80%	57.70%
IGK VJ, KDE+IgL	74%	86.50%	-
IGH FR3+IGK VJ	74%	81.10%	63.50%
IGH FR3+IGK VJ+KDE	79%	83.80%	67.30%

Table 2: Expanded consensus primers are comparing detection rates of BIOMED2 primers, Discovery, and Validation series in PCN population. BIOMED2 data from Liu et al. 2007, Br J Haemat, 138, 31-43 printed with permission of author.

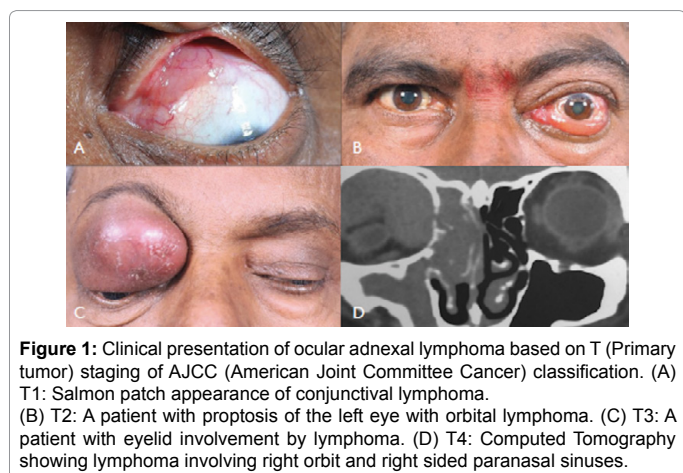


Figure 1: Clinical presentation of ocular adnexal lymphoma based on T (Primary tumor) staging of AJCC (American Joint Committee Cancer) classification. (A) T1: Salmon patch appearance of conjunctival lymphoma. (B) T2: A patient with proptosis of the left eye with orbital lymphoma. (C) T3: A patient with eyelid involvement by lymphoma. (D) T4: Computed Tomography showing lymphoma involving right orbit and right sided paranasal sinuses.

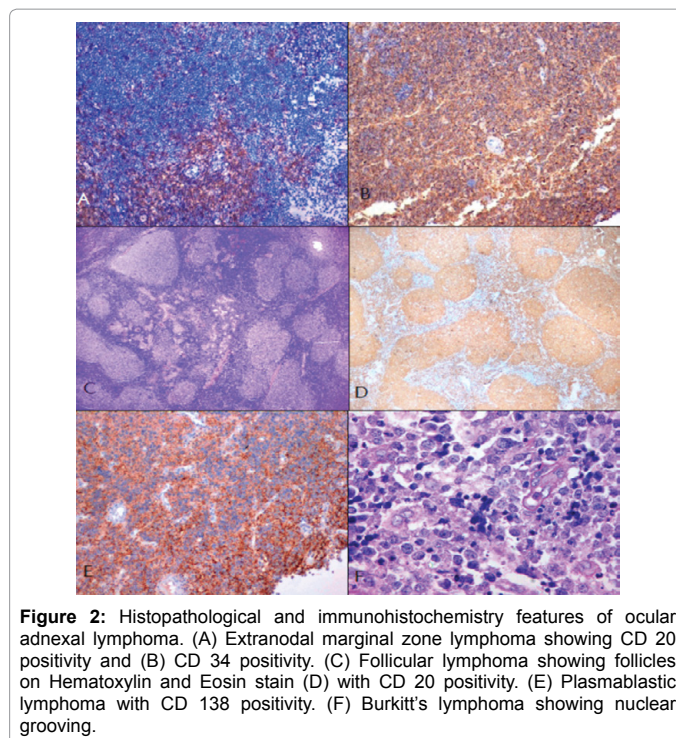


Figure 2: Histopathological and immunohistochemistry features of ocular adnexal lymphoma. (A) Extranodal marginal zone lymphoma showing CD 20 positivity and (B) CD 34 positivity. (C) Follicular lymphoma showing follicles on Hematoxylin and Eosin stain (D) with CD 20 positivity. (E) Plasmablastic lymphoma with CD 138 positivity. (F) Burkitt's lymphoma showing nuclear grooving.

Orbital OAL most commonly involves superior orbit. Depending upon its size and growth, it can cause proptosis, dystopia, motility restriction, and optic nerve compression. These masses on imaging show characteristic appearance of molding around the globe without any globe indentation or bone erosion. However certain malignant and rapidly progressing lymphomas such as mantle cell lymphoma, DLBCL<HIV related lymphoma may cause globe indentation, optic nerve compression, and bone erosion. Computed tomography (CT) or magnetic resonance imaging (MRI) helps in determining the location and extent of lymphoma.

Lacrimal sac lymphoma is rare but may account for up to 7.5% of all OAL cases [32]. It usually presents as swelling, epiphora, chronic dacryocystitis or sometimes blood-stained tears [33]. As compared to other OALs, DLBCL and MALT lymphoma are equally common in the lacrimal sac [33].

Other rare site of involvement is extraocular muscles [34]. Recti (73%) are most commonly involved muscles followed by obliques (17%) and levator (10%). Superior rectus is the commonest individual muscle affected by OAL followed by inferior and lateral recti [34].

Pathologic Features and Survival Rates

In the past, pathological features of lymphoma, benign reactive lymphoid hyperplasia (BRLH) and non-specific orbital inflammatory disease (NSOID) have been confused and often led to misdiagnosis. Grossly abundant monomorphous population of lymphocytes, scant interstitial matrix and absence of clear differentiation within germinal centers characterize lymphomas. BRLH has clear distinct germinal centers comprising of well-differentiated core and mantle cell zone. NSOID typically have abundant interstitial matrix or collagen with sparse number of cells. Most commonly occurring OALs typically are composed of monotypic-B cells, while NSOID and BRLH have preponderance of T-cells [1,2]. Feature on light microscopy is the presence of intranuclear cytoplasmic inclusion bodies called Dutcher

bodies, which are composed of immunoglobulins and are seen in about one-third of lymphoproliferative lesions but never in polyclonal lesions. Other feature of OAL is presence of multinucleated cells with or without abortive/residual germinal centers. However, many lesions may have indeterminate or borderline cytomorphological features and are difficult to differentiate in between these spectrum of disorders. With the advent of immunohistochemical (IHC) markers and genetic analysis, the identification of subtype and subpopulation of lymphocytes can now be determined accurately. Table 2 shows the typical IHC features of the common OALs.

EMZL or MALT lymphoma is the most common type of OAL seen in about 50% of cases [1,35]. EMZL is most commonly seen in the orbit (60%) followed by conjunctiva (33%), lacrimal gland (4%), and eyelid (3%) [36]. Although eyelid involvement is the least common, its association with systemic disease is highest ranging from 67% to almost 100% [36,37]. EMZL appears as expansion of marginal zone composed of monomorphic B-cells, plasmacytoid cells with occasional blast cells, and possible follicular colonization and lymphoepithelial lesions [19,36]. EMZL usually has indolent course with excellent prognosis but relapses may be seen. 5-year progression free survival and overall survival rate is about 71% and 75% respectively [36].

Follicular lymphoma is the second most common OAL accounting for up to 20% cases [1,35,38] and is the most common type of systemic lymphoma that secondarily affects ocular and adnexal tissues. The most common site of involvement with follicular lymphoma is conjunctiva (29%) followed by orbit (26%), lacrimal gland (26%), eyelid (6%), lacrimal sac (2%) and multiple sites (10%) [39]. Histologically it is seen as follicular growth pattern in about 70% cases and remaining have predominantly diffuse pattern [38]. In large multicenter international study consisting of 98 follicular OALs, disease survival and progression rate was independent of the type of growth pattern [39]. Other features include monomorphic germinal centers with loss of zonation, absence of macrophages and indistinct/absent follicle mantle. Overall 10-years survival rate is about 60% [39].

DLBCL is the third most common OAL and comprises of about 5% to 15% of all cases [35,37,38]. It occurs most frequently in orbit (49%) followed by conjunctiva (35%), lacrimal gland (18%), eyelid (15%) and lacrimal sac (1%) [40]. On histology, it has diffuse growth pattern with following variants: centroblastic (90%), immunoblastic, centroimmunoblastic, anaplastic and T-cell rich. Survival and prognosis is independent and unrelated to morphologic variant [40]. Recurrence and progression of disease in spite of treatment can occur in up to 60% of the patients. Overall survival and disease-specific survival rate for DLBCL is 36% and 47% respectively at 5-years follow up [40].

Mantle cell lymphomas are rare (<5%) and consist of small monomorphic cells, eosinophilic histiocytes, and germinal centers. The most common site of involvement is orbit (71%) followed by eyelid (64%) [41]. These tumors are more commonly seen in elderly males and are associated with systemic involvement in high proportions of cases. Overall survival rate is poor ranging from 8% to 39% but combined treatment with rituximab and chemotherapy can improve 5-years survival rate up to 83% [41,42].

Radiologic Features

Imaging not only helps in identifying the extent and location of the lesion but also helps in planning out the surgical approach and rule out deeper tissue involvement in conjunctival/eyelid OALs [43]. Non-contrast CT is usually requested in most cases as primary modality. Lymphomas are typically seen as well circumscribed, homogenous,

Tumor Burden	Discovery		Validation		Combination	
0%-1%	1/2	50.0%	0/3	0%	1/5	20.0%
>1%-10%	4/7	57.1%	6/12	50%	10/19	52.6%
>10%-50%	4/5	80.0%	11/17	64.7%	23/32	71.9%
>50%-100%	12/12	100.0%	8/8	100%	20/20	100.0%

Table 3: The tumor burden percentage by flow and/or microscopy vs detection rates of plasma cell neoplasm in discovery and validation series using the IG rearrangement PCR clonality study. A selection bias to have tumor burdens >50% in the discovery series is responsible for the higher sensitivity of the assay in the discovery series when compared with the validation series. The combination of the discovery and validation is reported.

hyper to iso-dense lesion and because of tissue composition usually mold around the globe and other orbital structures [44]. They are also described as oblong tumors, which tend to spread in fascial planes forming a pancake like configuration [45]. Tissue invasion and bony changes are rarely seen except for certain highly malignant OALs such as DLBCL and mantle cell lymphoma. In a large series evaluating the imaging of OALs, orbit (78%) was the most common location followed by conjunctiva (9%), lacrimal sac (9%), and eyelid (5%) [44]. CT has advantage over MRI that it can demonstrate certain atypical features like bony erosions or calcification.

MRI can be utilized for lesions that have extension in to brain, sinuses or are closely related to optic nerve causing diagnostic dilemma [44]. Lymphomas usually are iso-intense on both T1 and T2 weighted images and shows moderate enhancement with gadolinium (Table 3).

Differential Diagnosis

As all other orbital lesions, OAL has extensive differential diagnoses. Reactive lymphoid hyperplasia is difficult to differentiate both clinically and histopathologically. Other conditions include lacrimal gland benign and malignant tumors, nonspecific orbital inflammatory disease, leukemic infiltrates, infections, vascular tumors, and orbital metastases. Conjunctival masses may mimic amelanotic melanoma, age-related sub-conjunctival fat prolapse and certain other rare conjunctival tumors such as myxoma, juvenile xanthogranuloma and leiomyosarcoma. Eyelid lesions differentials include neurofibroma, vascular tumors, xanthogranuloma, and granulomatous diseases.

Systemic Evaluation

OAL represents extranodal lymphomas, as there is no lymphoid tissue in orbit, eyelid and conjunctiva. However lacrimal gland and conjunctival substantia propria possess lymphocytes. Whether OAL occurs as primary disease or secondary to systemic disease remains controversial. In a landmark study by Jakobeic and Knowles, 13% of patients diagnosed with OAL had past history of systemic lymphoma and on follow-up systemic involvement can develop in about 20% to 25% cases over 5 years [37]. There can be involvement of non-contiguous tissues (e.g. parotid glands, submandibular gland, lung, liver, spleen, kidney, breast), local/distant lymph nodes, and/or involvement of bone marrow. A thorough physical examination by medical oncologist is mandatory to detect systemic symptoms and signs of lymphoma. Bone marrow biopsy or aspiration is positive for lymphoma cells in about 5% to 10% of patients at the time of presentation [46]. TNM staging helps in documentation of initial systemic involvement especially occult disease, if present.

A case of OAL should be thoroughly investigated to rule out systemic disease not only at initial presentation but also during follow-up visits. Basic hematologic investigations such as complete blood count, peripheral blood smear, erythrocyte sedimentation rate, liver function tests and human immunodeficiency virus (HIV) serology should be

done. Others specific tests include serum lactate dehydrogenase (LDH) enzyme levels and serum electrophoresis (if plasma cells are noted on histology). Serum LDH helps in prognostication of disease and is raised in about 40% of patients with high-grade lymphoma and 15% with low-grade lymphoma [46].

Imaging for systemic evaluation includes chest X-ray, ultrasound abdomen for liver, spleen and abdominal lymph node enlargement. Recently FDG-PET (Fluorodeoxyglucose-Positron Emission Tomography) is becoming popular and is considered more sensitive than Gallium scan and whole body CT in detecting occult systemic disease [44]. It helps in both staging and monitoring of lymphoma. Although PET scan is most suitable for systemic involvement compared to traditional imaging, but it may interfere with proper evaluation of orbital tissues because of the following reasons: low resolution (5 mm to 7 mm cuts), proximity to the brain and presence of extraocular muscles having high metabolic activity.

Management

Management of OAL includes following: tissue diagnosis, staging, treatment, prognostication, and follow-up.

Tissue Diagnosis

Confirmation of the tissue diagnosis and identification of the subtype of OAL is crucial. Open biopsy is preferable as compared to fine needle aspiration cytology to allow for sufficient tissue specimen. For conjunctival lesions located in superior fornix, trans-conjunctival incision biopsy can yield sufficient tissue. For eyelid and orbital lesions, transcutaneous approach for may be utilized. In cases with bilateral involvement, the site with larger mass and easy accessibility should be chosen. In a study evaluating clonal analysis of bilateral, recurrent and multifocal ocular adnexal lymphomas, lesions were noted to be consisting of same clones of lymphoma cells [47]. Tissues are sent in formalin for histopathology and as fresh tissue for flow cytometry and gene rearrangement studies.

Staging and systemic evaluation

As discussed in previous section, TNM staging helps in documenting the disease, prognostication, and planning out the treatment and follow-up. In a study, AJCC 7th edition T category was related to disease-free survival [48]. Patients with bilateral disease may have decreased disease-free survival as compared to unilateral cases [23,48]. Systemic evaluation is important, not only that one-third patients have systemic disease at presentation or during follow-up but those with systemic disease have significantly worse outcome [48]. Moreover, bilateral involvement at presentation is a significant risk factor for the development of systemic lymphoma with an estimate of 72% at 10-year follow-up compared to 33% for unilateral cases [49].

OAL and intraocular lymphoma may also co-exist [29,37,38,50]. It is important to thoroughly evaluate a case with dilated indirect ophthalmoscopy, ultrasound B scan and fluorescein angiography (FA) or indocyanine green (ICG), which may identify subtle findings of intraocular lymphoma.

Treatment

Treatment of OAL is evolving and depends upon the presentation, histologic subtype and systemic involvement. Orbital radiotherapy and systemic chemotherapy forms the mainstay of treatment. Newer treatment modalities include immunotherapy with interferon and anti-CD20 antibody rituximab that have been shown to be useful either

when used alone or in combination with chemotherapy or as radioimmunotherapy. More controversy exists whether to treat indolent OAL with observation or with antibiotics because of possible infectious basis [25,27,51].

Radiotherapy: External beam radiotherapy (EBRT): EBRT is given with either photons (gamma/X rays) or particles (protons/neutrons). Radiotherapy is most commonly used modality to treat OAL without any systemic involvement. In case of systemic involvement or secondary lymphoma, radiotherapy is usually combined with chemotherapy or immunotherapy. OALs are radiosensitive tumors and the effective EBRT dose ranges from 25-30 Gy for low grade OAL and 30-40 Gy for high grade OAL. Several studies have demonstrated that the long-term local response rates for OAL with EBRT is 90% to 100% at 5 to 10-years follow-up [52-54]. Current evidence in literature suggests 30 Gy as the optimal dose for OAL [53,54].

Response to EBRT may vary depending upon the histological type. Initially it was thought that EMZL has better response and more favorable treatment outcomes with EBRT as compared to other types [55]. However recent studies have shown that EBRT alone in patients with primary follicular OAL can achieve 94% disease-free survival rate at 10 years [39]. For DLBCL, combination of radiotherapy with chemotherapy and rituximab can achieve disease-free survival in up to 95% cases [56].

Recurrence after local EBRT to orbit has been observed not only in the same orbit but also other non-contiguous structures such as locoregional lymph nodes, contralateral orbit and other extranodal sites [54,57]. These findings suggest that the role of EBRT may be uncertain on overall clinical course and disease outcome. A lifelong follow-up is essential to look not only for orbital recurrence but also delayed systemic occurrence.

In a recent study assessing the radiotherapy and prognostic effect based on AJCC 7th edition TNM staging, it was shown that although radiotherapy achieved excellent local control and survival rates, the TNM clinical staging system was not significantly predictive for progression free survival [58].

Side-effects of conventional EBRT can be either immediate in the form of conjunctival congestion or skin erythema or delayed including cataract, dry eye and radiation retinopathy/maculopathy/papillopathy. With higher doses more than 36 Gy, severe visual loss can occur from optic neuropathy, ischemic retinopathy, corneal ulceration, and neo-vascular glaucoma [59]. It's important for all the patients undergoing radiotherapy to be continuously monitored for these side effects. Intensity modulated radiotherapy (IMRT) or image guided radiotherapy utilizes 3-dimensional treatment zone which is more precise with fewer local side effects compared to conventional EBRT.

Systemic chemotherapy: Systemic chemotherapy is indicated in presence of systemic involvement or sometimes in cases with extensive orbital and adjacent tissue involvement with high grade malignant OALs such as DLBCL, mantle cell lymphoma, and small lymphocytic lymphoma [41,42,56]. Chemotherapy in such cases when combined with local radiotherapy to orbit has synergistic effect. Standard regimen consisting of cyclophosphamide, adriamycin, vincristine, prednisone (CHOP regimen) is most commonly used. Other alternative drugs include chlorambucil, purine analogues such as fludarabine and cladarabine, and C-MOPP regimen (cyclophosphamide, vincristine, procarbazine, prednisone). Very few studies have evaluated chemotherapy as a primary treatment modality for isolated OAL probably because EBRT has high success rate and the fact that

chemotherapeutic agents have systemic cytotoxic effects. When used as a primary treatment, initial response rate with chemotherapy may be as high as 100% with low-grade lymphoma, but recurrence may be seen in one-third of cases requiring salvage radiotherapy [59].

Immunotherapy: The two drugs that have been used for OALs are interferon-alpha (IFN- α) and anti-lymphocyte antibody rituximab [60-63]. IFN- α is used as a sub-conjunctival injection for conjunctival EMZL in patients without systemic involvement. There are two series from the same authors with both short-term and long-term follow-up and others have been mainly case reports [60,61,64-66]. IFN- α is used with dose of 1.5 million units injected 3 times weekly for 4 weeks [60,61]. Long-term results have shown that local disease control was achieved in 85% cases at median follow-up of 5 years.

Rituximab is an anti-lymphocyte antibody that binds against CD20 surface antigen that is expressed on 90% of malignant B-cells and causes destruction of B-cells with complement-mediated pathways, antibody-mediated destruction, induction of apoptosis and inhibition of cell proliferation [67]. It has been described both as intralesional/orbital injection and as intravenous injection for the treatment of EMZL [62,63,67-69]. Rituximab can be used as monotherapy or in combination with chemotherapy or radiotherapy [70,71]. Response with rituximab alone may be seen initially in almost all cases, but over long-term follow-up about one-third patients may have recurrences [69]. However, when used in combination with radiotherapy or chemotherapy, patients have better recurrence-free survival than radiotherapy alone achieving remission in up to 89% cases at 2 years follow-up [71,72]. Particularly for mantle cell lymphoma, combining rituximab with chemotherapy had significantly better overall survival rate than patients receiving chemotherapy alone (83% vs 8%) [41,42].

Radioimmunotherapy: Radioimmunotherapy consists of combining radioisotope to monoclonal antibody such as rituximab [73]. Advantages include directing radioisotope to bind to tumor B-cells and thus maximizing the radiation to tumor cells and avoiding critical organs such as bone marrow. The most commonly used radioisotope is yttrium 90 (Y^{90})-ibritumomab tiuxetan (Zevalin) and Iodine (I^{131}). Radioimmunotherapy has been US food and drug administration approved for the treatment of relapse/refractory, low grade, NHL including rituximab refractory disease [74]. It's also used as frontline treatment for the low grade EMZL and follicular cell OALs. Esmaeli et al. observed complete response in 10 out of 12 cases (83%) and partial response in 2 (17%) cases at a median follow-up of 20 months [73]. One case, which showed partial response in their series, also received radiotherapy at 6 months after the treatment. The most common side effect observed was transient mild pancytopenia, which lasted for 3 months. The total estimated dose delivered to the tissues was <3 Gy (1/10 of usual EBRT dose) [73].

Antimicrobial treatment: Chronic infection by *Helicobacter pylori* and *Chlamydia psittaci* has been implicated in the pathogenesis of OAL based on infection-inflammation-mutation (IIM) model [25-27]. In a phase II trial, 34 patients of EMZL with positivity for *Chlamydia psittaci* were treated with oral doxycycline monotherapy [75]. Complete response was seen in 6/34 (17%), partial response in 16/34 (47%), stable disease in 11/34 (32%), and one case (3%) had progressive disease at a median follow-up of 37 months [75]. Five-year progression free survival was noted in 55% cases. Because of fewer studies, variable results, and concern regarding the lack of association between *Chlamydia* and OALs, antimicrobial treatment cannot be at present considered as standard for the treatment of OALs [26,76,77].

Prognostic factors

(a) Age: Increasing age at >60 years has been noted to be associated with significantly increased local recurrence, occurrence of systemic lymphoma and lymphoma-related death by multi-variate analysis in a study [35].

(b) Site of involvement: Eyelid lymphomas have more aggressive course and are associated with increased incidence of systemic lymphoma as compared to orbital and conjunctival OALs. Eyelid OALs have systemic involvement in about 67% to 100% of cases compared to orbital OALs having 35% to 54% and conjunctival OALs having 20% to 38% incidence [37,78]. Lacrimal gland involvement was also seen to be associated with increased incidence of systemic lymphoma [77,79].

(c) Bilateral presentation: Patients with bilateral disease presentation have been observed to have significantly less 10-year survival rate as compared to cases with unilateral presentation [23,79].

(d) Clinical features: Clinical features such as symptoms <1 year, optic neuropathy, and pain at presentation are also related to increased lymphoma-related death [78].

(e) Prior or concurrent systemic lymphoma at presentation: Multiple studies have observed that systemic involvement with OAL is associated with poorer survival with increased rates of lymphoma-related death [1,3,13,19,23,37,79].

(f) TNM staging: Higher T-staging (5-year disease free survival rates: T1=67.8%, T2=59.2%, T3=28.6%, T4=33.3%; p=0.025) [48], involvement of nodes (N) and presence of distant metastasis (M) are associated with poor prognosis [22,23].

(g) Histopathology: Low grade lymphoma such as EMZL and follicular lymphoma have more favorable prognosis compared to higher grade lymphomas such as DLBCL, Mantle cell lymphoma and small lymphocytic lymphoma [1,3,79]. For EMZL, positivity for CD43 is a useful marker to identify the subset of patients that have poor prognosis [80].

(h) Genetic markers: Increased expression (>10% of tumor cells) of pRB, p53 and Bcl-6, and high tumor growth fractions indicated by MIB-1 are associated with poorer prognosis [78,79]. Increased expression of CD10, MUM-1 and Ki-67 are also noted to be poor prognostic markers [81,82].

(i) Serum LDH: An elevated serum LDH level is associated with poor prognosis. Serum LDH is raised in about 40% of patients with high-grade lymphoma and 15% with low-grade lymphoma [46].

Immunoglobulin G4 related disease and lymphoma

Immunoglobulin G4 (IgG4) related disease is a chronic sclerosing inflammatory condition that affects various body organs including orbit. It presents as non-specific orbital inflammatory disease [83]. Histological features include lymphoplasmacytic infiltration, fibrosis, phlebitis and presence of plasma cells positive for IgG4 immunoglobulin (>10/high power field or ratio of IgG4/IgG-positive cells >0.4:1) [84]. Majority of patients also have elevated serum IgG4 levels (>135 mg/dl) along with raised total immunoglobulin levels [84]. Cheuk et al. described three patients of lymphoma arising from IgG4-related dacryoadenitis and systemic IgG4 disease [85]. It was unclear whether lymphoma was de novo or from IgG4 sclerosing disease but neoplastic cells expressed IgG4. Nakayama et al. studied 12 patients histologically diagnosed as having orbital IgG4 disease and/or MALT lymphoma [86]. They noted that one patient definitely had concurrent

IgG4 and MALT lymphoma, while 4 cases had either probable/possible concurrent disease. Further long-term studies are needed to know the exact pathogenesis and relationship between the two.

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