10 Ocular Adnexal Lymphoma: Systemic Therapy and Clinical Trials

Allison Winter, Mary Aronow, Arun D. Singh, and Brian Hill

Introduction

Ocular adnexal lymphoma (OAL) is heterogeneous group of lymphomas, the majority of which are low-grade, indolent, B-cell, non-Hodgkin lymphomas (NHLs) [1]. OAL affects structures including the eyelids, conjunctiva, lacrimal apparatus, extraocular muscles, and sometimes the orbit. Disease may be limited to a single, localized tumor, or it may be multifocal. Overlap with ocular adnexal sites is common (10–20% of cases), and co-existing uveal involvement has been observed [2–6]. Moreover, OAL can affect regional, central, and peripheral lymph nodes as well as other distant extranodal sites. The 10-year, disease-specific mortality is approximately 5–10% [7]. Many of the advances in understanding OAL were initially demonstrated in systemic lymphoma (Box 10.1).

Box 10.1 Important Aspects of Ocular Adnexal Lymphoma (OAL)

- OAL consists primarily of five types of lymphoma, the most common of which is extranodal marginal zone type.
- The diagnosis depends on pathology, immunophenotypic analysis, and molecular genetics studies.
- Treatment of localized disease typically involves radiation therapy which results in excellent long-term local control.
- Systemic therapy with traditional chemotherapy or rituximab is reserved for aggressive histologic subtypes or those with systemic involvement.

Epidemiological Aspects

OAL is a rare disease, likely representing as many as 8% of all extranodal NHLs [1]. Its incidence is approximately 0.2 per 100,000 [8]. There is similar male and female predilection (60% of cases in most series) [9]. It affects most ethnic groups although there is significant geographic variation among systemic lymphoma, with the white population in the USA showing the highest incidence. The overall incidence of systemic OAL increases in a pattern which mirrors NHL [10].

A. Winter · B. Hill (✉)
Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: wintera2@ccf.org; hillb2@ccf.org

M. Aronow
Retina Service, Department of Ophthalmology, Massachusetts Eye and Ear/Harvard Medical School, Boston, MA, USA
e-mail: mary_aronow@meei.harvard.edu

A. D. Singh
Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: singha@ccf.org

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Among ophthalmic tumors, OAL comprises 6–8% of orbital and 10–15% of adnexal lesions [11–14]. Localized, ocular-only disease is present at diagnosis in 60–80% of cases, while the remainder have systemic involvement at the time of ophthalmic presentation [15, 16]. Bilateral disease is observed in 10–15% of individuals with ocular-only lymphoma [17]. Among affected ocular sites, the frequencies of involvement are conjunctiva 20–33%, orbit/lacrimal gland 46–74%, and eyelid 5–20% [7, 18]. Distinction between these sites can be difficult and combined involvement may be underreported [19, 20].

Many cases previously diagnosed as benign reactive lymphoid hyperplasia (BRLH) are now considered malignant lymphoma using current diagnostic techniques [21]. Retrospective studies of patients diagnosed with BRLH have revealed that up to 80% are now classified as malignant lymphoma [21]. At present, BRLH represents a minority of cases and is a diagnosis of exclusion.

Etiology and Pathogenesis: B-Cell Biology and Lymphomagenesis

The largest advances in understanding lymphoma pathogenesis and etiology as well as classification derive from the refined immunophenotypic [characterization of lymphocyte surface receptors, usually members of the clusters of differentiation (CD)] combined with concurrent advances in the understanding of molecular genetics of lymphocyte biology. This has resulted in a mechanistic hypothesis for lymphomagenesis which connects specific lymphoma types to different precursor cells and genetic events. Lymphoma classification, diagnosis, and pathogenesis are closely intertwined with their immunopathology and molecular biology.

The relationship between stages of lymphocyte development and their associated lymphoma diagnosis is based on distinct immunophenotypes. Tumors arise from germinal center cells (follicular lymphoma), cells of the mantle zone (mantle cell lymphoma), or memory B-cells (extranodal marginal zone lymphoma) all of which have undergone antigen exposure. From a molecular genetic standpoint, during normal lymphocyte maturation, somatic mutation may occur in which an antigen receptor gene region is juxtaposed to an oncogene region resulting in deregulation of the oncogenic region. Less often, a novel oncogenic protein is formed by fusion of two other genes. Chromosomal translocations underlying these alterations are well described in up to 90% of systemic lymphoma [22, 23]. Limited data suggests that these translocations are less common in OAL [24, 25].

The theory that lymphoma develops due to errors occurring during normal lymphocyte response to infection or inflammation is referred to as the infection/inflammation/mutation (IMM) model of lymphomagenesis. This has been corroborated in two ways. One is the recognized association of lymphoma with chronic antigen stimulation and infection, immune suppression, and autoimmune disease [26]. The prototypic example of the IMM model is gastric extranodal marginal zone lymphoma in which the endogenous mucosal-associated lymphoid tissue (MALT) develops lymphoma in response to chronic *H. pylori* infection. With the recent understanding that most OALs are also extranodal marginal zone lymphoma/MALT lymphomas, studies have shown evidence of DNA from infectious agents including *C. psittaci* and *H. pylori* in OAL [27, 28]. Infection as an underlying etiology for OAL shows variation among geographic regions and also within different series in the same geographic location [27, 29, 30]. Treatment implications of this are discussed below.

In addition to its therapeutic implications, perhaps the most important consequence of the IMM model is that it explains why the ocular adnexa, which has little if any endogenous lymphoid tissue, has lymphoma as its most common neoplasia. Similar mechanisms may occur in RLH. Based on the relative infrequency of OAL, there may be other factors required for lymphomagenesis.

Classification

OAL represents the malignant end of the spectrum of ocular adnexal lymphoproliferative disorders. As previously noted, BRLH and reactive lymphoid hyperplasia (RLH) with atypia represent a minority of cases and together comprise benign and intermediate forms of the disease, respectively [31, 32]. OAL is a localized form of lymphoma which has been integrated into the schema of lymphoproliferative diseases described in two major classification systems: the Revised European American Lymphoma classification in 1994 [33] and the 2008 World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissue [34].

OAL can be divided by the type and site(s) of tissue involvement. The vast majority of OAL are of the non-Hodgkin B-cell type. Despite the extensive numbers of systemic lymphoma subtypes, most OAL belong to one of the five subtypes: extranodal marginal zone (EMZL or MALT lymphoma), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), or lymphoplasmacytic lymphoma (LPL) (Table 10.1) [15, 20, 35–42]. The vast majority, approximately 80%, are of the EMZL type in most series [10].

OAL is termed solitary if it is the only site involved, secondary when contiguous sites are involved, and systemic if remote sites are involved. OAL is solitary in 60–80% of cases at the time of presentation [15, 35, 37, 42]. The rate of progression to systemic involvement can only be accurately identified using current criteria since misclassification was prevalent prior to the use of the WHO classification.

Table 10.1 Distribution of various types of ocular adnexal lymphoma

Author	Year	Patients	EMZL (%)	Follicular (%)	Mantle zone (%)	Lymphoplasmacytic (%)	Diffuse large B-Cell (%)	Plasmacytoma (%)	T-cell
White	1995	43	Not done						
Nakata	1999	44	77	–	4	2	14	–	–
Jenkins	2000	192	54	11	2	24	8		<1
McKelvie	2001	70	63	17	3		11		1
Shields	2001	117	Not done						
Mannami	2001	43	86	–	2	–	12	–	
Bhatia	2001	47	17	53			26		
Coupland	2003	230	59	12	3	4	13	4	3
Fung	2003	98	57	18	4		7		
Sharara	2003	17	47	12	18	6	18	–	
Cho	2003	57	98		2				
Sullivan	2005	69	35	22	1	4	7	3	6
Rosado	2006	62	89	–	–	–	<1	–	–
Ferry	2007	353	52	23	5	1	8	–	<1
Oh	2007	128	75	–	3	1	5	1	4
Hatef	2007	43	44	21	1	–	21	–	<1
Rootman	2011	122	60	12	1	4	4	–	–
Watkins	2011	57	28	2	5	–	4	4	5
Zanni	2012	41	63	10	5	5	17	–	–
Total		1833	17–98	11–53	1–18	4–24	1–26	1–4	1–6

Clinical Features

Symptoms

Subjective complaints in OAL are broad and may include: lacrimal gland, orbital, conjunctival mass or apparent eyelid mass, exophthalmos, pain, or diplopia. Many lesions are asymptomatic. If the lacrimal gland is involved, dry eye symptoms may occur.

Signs

OAL has site specific presentations which affect how the diagnosis is made. In the conjunctiva, lesions present typically with salmon or flesh pink color (Fig. 10.1). Clinical appearance does not allow distinction of benign from malignant lymphoproliferative disease. In the orbit, lacrimal gland, and eyelid, the lymphoma presents as a mass, which if palpable, is typically firm. Mobility is variable depending upon attachment to other structures. Diplopia may occur upon how rapidly the mass develops. Exophthalmos and decreased retropulsion of the globe may be the only clinical signs. Secondary ptosis may also occur (Fig. 10.2a). Involvement of the nasolacrimal drainage system can occur. Compression or invasion of the optic nerve can lead to vision loss. During orbital biopsy, OAL appears as a white to pink mass reflecting its leukocytic and vascular characteristics.

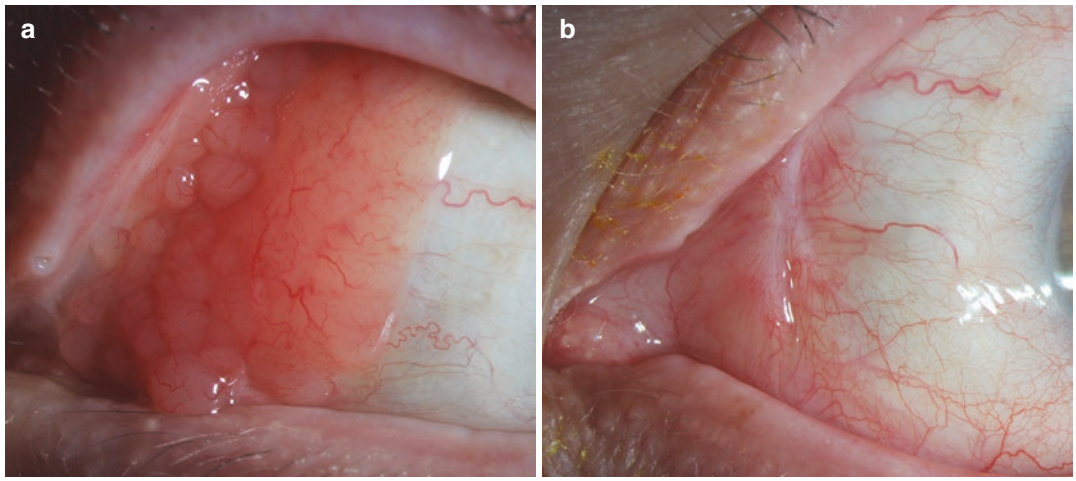

Fig. 10.1 Conjunctival lymphoma with typical salmon patch appearance (**a**). Note total regression following radiation therapy (24 Gy) (**b**)

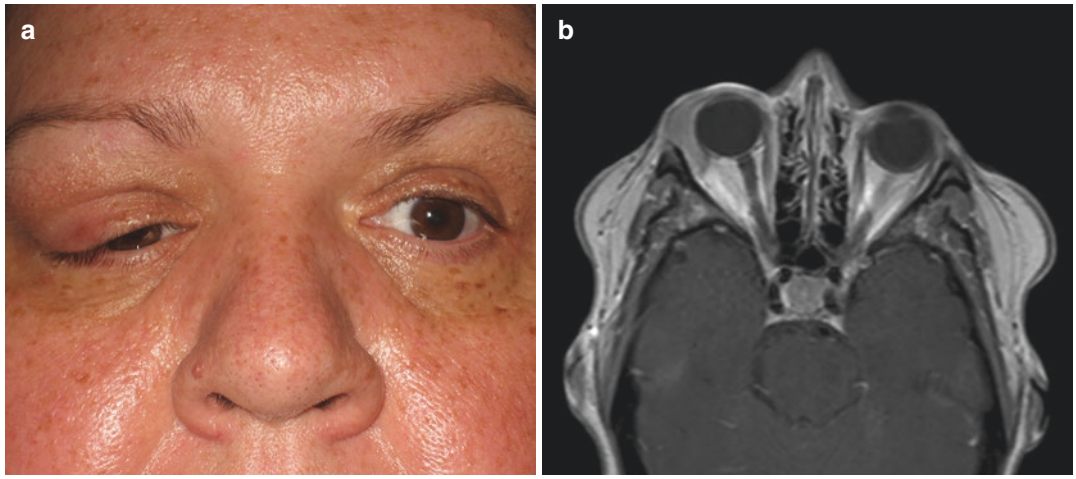

Fig. 10.2 Proptosis due to lymphoma involving the lacrimal gland (**a**). Coronal MRI scan (T-1 weighted image) demonstrating right orbital involvement (**b**). The infiltrating mass is in the existing normal anatomic spaces without distortion

Diagnostic Evaluation

Evaluation of OAL involves characterization of the lesion and staging. Biopsy should be obtained by open methods to allow sufficient material for multiple special studies: pathology, lymphocyte immunophenotypic analysis, and molecular genetic studies to identify gene rearrangements indicative of clonality and/or translocations.

Local Imaging Studies

Imaging studies of the orbit play an important role in OAL but are performed at different times depending on the presentation. With conjunctival disease, the lesion is frequently biopsied first and imaging of the orbit follows to assess orbital involvement. With orbital and lid disease, the orbit is usually imaged to optimize the biopsy process. Contrast enhanced CT and MRI scans of the orbits will show enhancing lesions which can be discrete or diffuse (Fig. 10.2b). Lymphoid lesions typically mold to structures such as the globe or bony orbit. Neuroimaging will reveal orbital lesions in up to 50% of clinically unsuspected cases [19]. Paranasal sinus involvement is not uncommon.

It is important to emphasize the frequency of overlap that occurs between OAL and uveal lymphoma [2–6]. For this reason, ancillary imaging studies such as B-scan ultrasonography and angiography are useful in characterizing the full extent and laterality of disease. This is particularly important in cases with subtle extrascleral extension (ESE) or occult involvement of the fellow eye. B-scan ultrasonography is a sensitive modality for detecting ESE. The pattern of ESE may be crescentic thickening, a discrete mass (often adjacent to the optic nerve), or diffuse choroidal thickening in cases where uveal lymphoma overlaps with OAL. Fluorescein (FA) and indocyanine green angiography (ICG) are also useful in suspected cases of uveal involvement. ICG demonstrates a characteristic pattern of focal hypofluorescence corresponding to clinically observed choroidal infiltrates. These foci may represent regions of choroidal nonperfusion sec-

ondary to space-occupying choroidal infiltration by lymphoma cells. ICG is superior to FA in visualizing the choroidal circulation and is therefore a particularly useful imaging modality in confirming the diagnosis and extent of disease burden [43]. When performed, FA may show early hyperfluorescence, hypofluorescent spots corresponding to clinically observed choroidal infiltrates, choroidal folds, or a normal angiogram.

Staging Procedures

Since OAL can co-exist with lymphoma in other sites, after OAL is classified, staging is performed. This includes a thorough physical examination by an experienced medical oncologist. Invasive staging has been replaced by the use of high resolution contrast enhanced imaging techniques: whole body PET/CDT or diagnostic CT of the chest, abdomen and pelvis, and MRI of the brain. Imaging of the neck is performed if cervical nodes are palpated or suspected to be enlarged. Laboratory evaluation includes complete blood count (CBC), hepatic enzymes, serum lactate dehydrogenase (LDH). Although part of the formal staging process for lymphoma, bone marrow aspiration, and biopsy has very low yield in patients with OAL. In the absence of cytopenias and radiographic evidence of systemic disease.

While not typically performed by the ophthalmologist, understanding the staging process is important for multidisciplinary management of OAL. The Ann Arbor staging system has several deficiencies for characterizing OAL, particularly as it results in a disproportionate staging distribution. Two-thirds of primary OAL cases present as a localized mass, which under the Ann Arbor system are classified as stage IE [15, 17, 44–48] (Table 10.2). Analysis can be challenging because of the use of different criteria but overall rates for initial staging are 60–80% for IE, 4–25% for IIE, and 16–18% for Stage III and IV combined [7, 36, 37]. Studies using criteria of extraorbital disease showed Stage III and IV rates of 22–36% at diagnosis [15, 35, 40]. This precludes the ability to differentiate the majority of OAL cases from one another based upon disease extent within the

Table 10.2 Staging of NHL by Ann Arbor and tumor-node-metastasis systems

Ann Arbor system	
Stage I	Localized or extranodal disease (Ann Arbor [AA] I or IE)
Stage II	2 or more nodal sites on same side of diaphragm
Stage III	2 or more nodal sites on both sides of diaphragm
Stage IV	Disseminated extranodal involvement (i.e. bone marrow, etc.)
B = B symptoms (unexplained fevers, drenching night sweats, or unintentional loss of >10% body weight) E = Extranodal involvement (visceral organ, ocular structures, skeletal lesions, etc.)	
Tumor-node-metastasis system[a]	
T Classification	TX Lymphoma extent not specified
	T0 No evidence of lymphoma
	T1 Conjunctival lymphoma alone
	T2 Orbital lymphoma with or without conjunctival involvement
	T3 Preseptal eyelid lymphoma in addition to conjunctival/orbital disease
	T4 Invasion of adjacent structures, such as bone and brain
N Classification	NX Lymph node involvement 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
M Classification	MX Lymphoma dissemination not assessed
	M0 No evidence of involvement of additional extranodal sites
	M1 Lymphoma involvement of other organs (at diagnosis or subsequently)

[a] Modified from the American Joint Committee on Cancer (AJCC) seventh edition TNM-based staging manual for OAL

ocular adnexal structures which may have important prognostic implications [18, 49].

More recently, a tumor-node-metastasis (TNM) based staging system for primary OAL has been developed under the guidance of the American Joint Committee on Cancer (AJCC) [50, 51]. (Table 10.2). This system addresses many of the shortcomings of the Ann Arbor system and more precisely defines disease extent. The ultimate goal of the proposed TNM-based system is to facilitate future studies aimed at identifying clinical and histopathologic features of OAL of prognostic significance and to assess treatment outcomes. To date, the feasibility of this system has only been analyzed in a limited capacity [52].

Differential Diagnosis

The clinical and imaging differential diagnosis of OAL is extensive, due to the paucity of specific features. It includes inflammatory lesions, benign lymphoproliferative lesions [32], epithelial tumors, melanocytic tumors, infectious lesions, and lacrimal gland lesions of the conjunctiva. In the orbit and lid, any mass including metastases, dacryoadenitis, inflammations, and other benign and malignant tumors must be considered.

Pathologic Features

Pathologic analysis can identify obvious lymphomas but cannot reliably differentiate lymphoma types (Fig. 10.3). Recent data has shown that using the current WHO classification, 76% of lesions previously classified as RLH are now reclassified as lymphomas. This is due to the recognition that a small number of malignant lymphocytes, whose presence is indicative of lymphoma, can be overshadowed by surrounding normal or reactive lymphoid cells. Immunohistochemistry can be carried out qualitatively on tissue sections or quantitatively on dispersed cells (flow cytometry). The use of intact tissue allows localization of marker expression, which can be critical in making the correct diagnosis. For example, overexpression of cytoplasmic Bcl-2 is not seen in normal follicular structures and is consistent with follicular lymphoma [32]. Immunohistochemistry, however, may not detect such critically important cells when sampling effect limits their presence. Flow cytometry, in contrast, does not give anatomic information but can accurately assign the immunophenotype of involved cells with very small amounts of specimen.

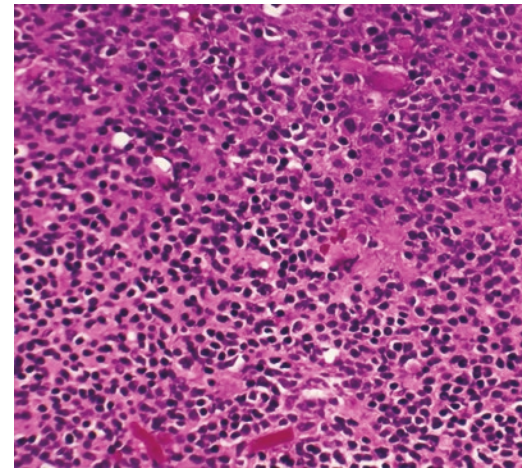

Fig. 10.3 Photomicrograph of monomorphic lymphocytes typical of EMZL type ocular adnexal lymphoma. (H&E, Original magnification × 100. Reproduced with permission from: Aronow ME, Hill BT, Singh AD. Orbital and adnexal lymphoma. Pe'er J, Singh AD (Editors) Clinical Ophthalmic Oncology. Volume 4, Chapter 15, Springer, Heidelberg (2019))

Molecular genetic analysis of OAL is important in two ways. Identification of overexpressed heavy chain gene rearrangements is indicative of clonality and typically represents malignancy. Tumor cells can be analyzed for translocations which may be indicative of a specific lymphoma type. Translocation of the MALT gene with API2 [t(11;18)(q21;q21)] is of specific interest since its presence is generally associated with more aggressive disease [53]. The expansion of the tools for lymphocyte characterization has paradoxically increased the chances for contradictory or incomplete characterizations using the new criteria. In such situations, the wisdom of an experienced hematopathologist is critical, though some lesions will remain unclassifiable.

Rare Variants

There are several rare variants and simulating conditions of OAL such as Langerhans cell histiocytosis (LCH), Rosai-Dorfman disease, T-cell lymphoma, T-cell/natural killer (NK)-cell lymphoma (lethal midline granuloma), and Burkitt lymphoma that we have included in this review.

Langerhans Cell Histiocytosis

LCH is characterized by a proliferation of Langerhans cells and inflammatory cells that generally affects children and young adults. The disease may be localized or it may affect multiple systems including the skin, bone, lungs, and lymphatics. Ophthalmic disease is observed in 10–23% of cases and most often manifests as a solitary lesion within the orbit; however, intraocular involvement in the form of an atrophic retinochoroidopathy has been reported [54–56]. Confirmation of diagnosis is made by biopsy, which demonstrates numerous histiocytes, giant cell formation, and eosinophilic granulocytes. Transmission electron microscopy (TEM) reveals characteristic intracytoplasmic Birbeck granules [55].

Rosai-Dorfman Syndrome

Also labeled as sinus histiocytosis with massive lymphadenopathy is a benign form of idiopathic histiocytosis that typically affects children and young adults. The majority of individuals (approximately 80%) develop painless cervical lymphadenopathy [57]. Extranodal involvement may affect multiple systems including the respiratory tract, skin, bones, visceral organs, and the central nervous system. The disease has multiple ophthalmic manifestations including lesions within the orbit, eyelid, and lacrimal apparatus. Compressive optic neuropathy, uveitic glaucoma, serous retinal detachment, and marginal corneal infiltrates have been reported [58]. Ocular adnexal involvement occurs in approximately 10% of patients with extranodal disease [59].

T-Cell Lymphoma

In rare cases, OAL can be of T-cell origin. In a review of 353 individuals with OAL, only a single case (0.3%) was of T-cell lineage [17]. As with B-cell neoplasms, a heterogeneous group of T-cell lymphomas can involve the ocular adnexal structures. Most T-cell lymphomas affecting the ocular adnexal structures are aggressive and carry a poor prognosis.

Most non-B-cell lymphomas are an extension of the malignant stage of mycosis fungoides or a secondary manifestation of systemic T-cell lymphoma. In a series of seven individuals with OAL of T-cell origin, three cases were peripheral T-cell lymphomas (PTCL) demonstrating positivity for CD3, CD8, and βF1 and negativity for CD56. Two cases were positive for CD3 and CD30 while negative for CD56 and were classified as anaplastic large-cell lymphomas of T-cell type (T-ALCL) [60]. The remaining two cases were positive for CD3 and CD56 and negative for βF1. These two cases were positive for Epstein-Barr virus (EBV) by in situ hybridization, consistent with T-cell/natural killer (NK)-cell lymphoma of nasal type (also referred to as lethal midline granuloma) [60, 61].

Burkitt Lymphoma

Burkitt lymphoma is a rare entity associated with translocation between chromosomes 8 and 14 affecting c-myc [62]. Three forms, all of which may affect the orbit, have been described. The African type frequently involves the orbits and maxillary bones and is associated with the presence of antibodies against Epstein-Barr virus (EBV) antigens [62]. The non-African type usually affects lymph nodes, bone marrow, and viscera. The third form affects immunocompromised individuals and is associated with acquired immunodeficiency syndrome (AIDS) [63–65]. Recent review of 16 immunocompetent individuals with sporadic orbital Burkitt lymphoma revealed a median age at diagnosis of 12 years [66]. Presenting symptoms included proptosis, oph-

thalmoplegia, and eyelid edema. Fourteen (88%) in this series had systemic involvement [66]. Biopsy of orbital lesions reveals a characteristic "starry-sky" appearance associated with Burkitt lymphoma [65]. Prognosis is guarded for this extremely aggressive lymphoma as significant mortality (54%) is observed within 1 year of presentation [66].

Treatment

The treatment of OAL is an area of controversy, progress, and change. Currently OAL treatment depends on whether the disease is localized or systemic. Local disease can be very effectively treated with radiation alone. Systemic disease is frequently treated in a manner similar to other indolent lymphomas, typically using rituximab alone or in combination with cytotoxic chemotherapy. With the recognition that the vast majority of OALs are of the EMZL/MALT type and that there may be an infectious basis for this subgroup of OAL, there is possibility of deferring cytotoxic modalities. A second controversy is whether to treat indolent OAL. A survey of treatment modalities follows.

Surgery

Surgery has been reported to be successful in managing certain cases of highly localized OAL and has been recommended for Stage I MALT systemic lymphoma in some sites. Its applicability remains dubious for most OAL due to the diffuse nature and frequent juxtaposition of OAL to sensitive ocular tissues. Surgery should therefore be reserved for localized, isolated lesions of the conjunctiva [7, 19].

Cryotherapy

Cryotherapeutic ablation of OAL has limited use in the management of OAL. It has resulted in variable success due to debulking the tumor without complete elimination of malignant tissue. It may have application in a limited number of patients with conjunctival OAL who are unable to receive other treatment modalities [20].

Radiation

Historically, external beam radiation (EBRT) has been the most frequently used modality for treatment of OAL. Analysis of this modality is confounded by small patient numbers in most series, the use of early and inaccurate classification schemes, short follow-up times, and apparent lack of ophthalmic follow-up. Complications were detected at a rate of up to 50% higher when close ophthalmic follow-up was performed.

Both electron and photon irradiation have been successfully employed in OAL. Dosage is based on the tumor grade or type [15, 35, 38]. Typical doses are 28–36 Gy for low-grade OAL and 30–40 Gy for high grade OAL. The role of lens shielding to decrease cataract formation is controversial with some studies showing no effect on local recurrence and others showing recurrences occurring in patients who underwent lens-sparing radiation treatment protocols [67, 68].

Analysis of radiation dose–response relationship of EMZL revealed that 5-year local tumor control rates of EMZL were 81% with doses below 30 Gy but 100% with doses higher than 30 Gy [69]. Variable sensitivity to radiotherapy based upon lymphoma subtype was observed as follicular lymphoma showed a 100% response rate to both high and low doses. While radiation studies frequently emphasize the ability to obtain local control, population-based observational data suggests that radiation may confer a survival benefit [70]. Even Stage IV-EA disease showed good local control, though survival was significantly lower. Multiple studies revealing higher rates of delayed systemic recurrence suggest that longer follow-up is necessary for accurate assessment of treatment effect [15].

Chemotherapy

Since OAL frequently presents as localized disease (stage IE), chemotherapy is rarely used, with the exception of aggressive DLBCL [71]. The review of chemotherapy used in lymphoma is beyond the scope of this chapter. Standard chemotherapy for OAL when it is part of more advanced disease is that of standard systemic lymphoma regimens using single agent rituximab alone or in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), the alkylating agent chlorambucil and more recently, bendamustine which has dual properties of an alkylating agent and a purine analogue. While some have used systemic corticosteroids for tumor suppression of OAL, steroids offer ineffective long-term control.

Immunotherapy

Interferon

Interferon (IFN-alpha) has been used rarely for OAL despite its long standing use in systemic lymphoma. One report of five cases showed 80% initial complete response with short term follow-up [72]. One patient with Stage IIA disease died of systemic lymphoma at 1 year. More data regarding local and systemic efficacy are needed prior to acceptance of this modality.

Rituximab

Anti-lymphocyte antibodies are a recent form of lymphoma treatment. The most commonly used has been an antibody to CD20, rituximab, which leads to destruction of B-cells using mechanisms of complement and antibody mediated destruction as well as induction of apoptosis. These antibodies are effective when used alone but also significantly increase the remission rates when used in combination with chemotherapy [73].

Antimicrobial Treatment

A recent development in OAL management is based on the IMM model of lymphomagenesis. There is increasing evidence of the role of chronic infection in OAL. Both *C. psittaci* and *H. pylori* have been implicated [27, 28]. Follow-up data from *C. psittaci* detection studies have suggested a therapeutic effect following antibiotic therapy with doxycycline, presumably by eradication of the infection which underlies lymphomagenesis. Other studies have shown an effect in small numbers of patients using anti-*H. pylori* triple therapy [74]. Overall, antibiotic treatment regimens have shown variable results by study group and geographic location [30, 75]. Larger studies are needed to clarify the role of antibiotics in treatment of OAL.

Prognosis

Prognosis of OAL is evaluated in three ways: local control, systemic involvement, and death from lymphoma. Excellent local control has been reported using external beam radiation. Among OAL, EMZL has a quantitatively better prognosis than other tumor types with regard to spread of tumor and lymphoma related death, though the risk ratio was similar among the milder forms EMZL, LPCL, and FCL. The mortality ranges were: EMZL 0–20%, DLBCL 25–75%, FL 20–37%, MCL 38–100%, LPL 14–100% [7, 15, 35, 36].

Extraorbital spread can occur in over 45% of EMZL patients with mean follow-up of 63 months, suggesting that longer follow-up is needed [15]. Patients with indolent disease may survive decades without treatment.

Future Research

Future research will be focused on the mechanisms of lymphomagenesis to determine whether prelymphomatous conditions can be detected and treated with less toxic methods. One key question is whether the role of infectious agents will be as important as in gastric lymphoma where it has revolutionized care. Understanding lymphomagenesis may also allow for more targeted therapeutic agents.

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