Lymphomas involving the eye and the ocular adnexa
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Purpose of review
To describe recent advances in the understanding of the pathogenesis of the most common malignant lymphomas that occur as primary and secondary tumors in ocular tissues.

Recent findings
Advances have been made in the understanding of the genetic alterations in mucosa-associated lymphoid tissue lymphomas, including various chromosomal translocations, such as the most recently described t(3;14)(p14.1;q32) involving the FOXP1 gene. Further, the development of ocular adenexal mucosa-associated lymphoid tissue lymphomas has been associated with Chlamydia psittaci in some geographic areas. Subdivision of diffuse large B-cell lymphoma into clinically prognostic groups had been achieved on the basis of gene expression profiles using complementary DNA microarrays. Tumor-infiltrating cells, such as macrophages, have been demonstrated to be of prognostic significance in follicular lymphoma.

Summary
Understanding of the ocular adnexal and intraocular lymphomas has advanced with progress in lymphoma classification systems, namely the World Health Organization lymphoma classification. This knowledge is being fine tuned with advances in technology, such as complementary DNA microarrays. The clinical significance of this scientific progress has yet to be determined.

Keywords
diffuse large B-cell lymphoma, follicular lymphoma, intraocular lymphoma, mucosa-associated lymphoid tissue lymphoma, non-Hodgkin lymphoma, ocular adnexal lymphoma

Introduction
The lymphomas are malignant neoplasms derived from a clonal proliferation of B or T lymphocytes. They can be divided into two major groups: Hodgkin lymphoma and non-Hodgkin lymphoma (NHL) [1]. The NHLs are a large heterogeneous group of neoplasms that can be further subdivided according to the cell of origin. About 80% of NHLs arise from B lymphocytes or their precursors, 14% develop from T cells, and 6% from natural killer cells [1].

For many years, the Working Formulation [2] and the Kiel lymphoma classification [3] were used predominantly in America and Europe, respectively. In 1994, the International Lymphoma Study Group [4] established the Revised European American Lymphoma (REAL) classification, which incorporated elements of both classification systems and was based on the morphologic, immunophenotypic and genetic, and clinical features of the various lymphoma entities. It was the first lymphoma classification that included both nodal and extranodal tumors. Owing to its high degree of reproducibility, the REAL classification has now been updated under the auspices of the World Health Organization (WHO) and is called the WHO Lymphoma Classification [1].

Lymphomas of the eye and its adnexa are relatively uncommon, accounting for approximately 10% of all extranodal malignant lymphomas [5]. Most are primary tumors and are usually NHLs of B-cell type: the most common primary lymphoma subtype occurring in the ocular adnexa is the low-grade malignant extranodal marginal zone B-cell lymphoma of MALT type (mucosa-associated lymphoid tissue) [6–8]. The most common lymphoma arising from ocular tissues is the so-called primary intraocular lymphoma, which is a diffuse large B-cell lymphoma (DLBCL) of high-grade malignancy arising in the retina [9]. Secondary ophthalmic
lymphoma, which arises from systemic disease, can occur both in the ocular adnexa and intraocularly [10]. The most common secondary lymphoma subtype occurring in the ocular adnexa is follicular lymphoma, and that most frequently occurring in tissues within the eye is DLBCL.

In this review, we briefly describe the most recent advances in the understanding of the most common and important types of B-NHL occurring in ophthalmic tissues, i.e. the MALT lymphomas, the DLBCL, and follicular lymphomas. Additional varied secondary ophthalmic manifestations of lymphomas are also summarized.

Extraocular lymphomas: primary tumors

The three most frequent primary B-NHLs of the ocular adnexa are briefly discussed in order of frequency.

Mucosa-associated lymphoid tissue lymphomas

The MALT lymphomas are low-grade B-cell lymphomas that occur mostly in the gastrointestinal tract, particularly in the stomach. Since their first description by Isaacson and Wright [11] in 1983, it has become apparent that MALT lymphomas arise in a variety of extranodal sites, such as the salivary glands, thyroid, skin, ocular adnexa, lung and urogenital tract. Regardless of the site of origin, MALT lymphomas have similar clinical, pathologic, and molecular features (Table 1) [12].

Recently, several cytogenetic alterations have been demonstrated in MALT lymphomas, including those occurring as either primary or secondary tumors in the ocular adnexa (Table 1) [12,13**]. Most affect a common signaling pathway and, thus, share a common pathogenesis. The common karyotypic alterations that characterize MALT lymphomas include trisomies 3 and 18 as well as the translocations t(11;18)(q21;q21), t(14;18)(q32;q21), t(1;14)(p22;q32), and the newly discovered t(5;14)(p14.1;q32) involving the FOXP1 gene [12,13**]. The frequency of these translocations in MALT lymphoma is summarized in Table 1. These chromosomal alterations have proven to be of prognostic significance, particularly in gastric MALT lymphomas. It remains to be determined whether particular chromosomal abnormalities occur in primary ocular adnexal MALT lymphomas, and others in secondary ones. In addition, the chromosomal translocations are yet to be correlated with location (e.g. conjunctiva versus orbit), and their prognostic value in ocular adnexal lymphoma (OAL) is still to be determined.

Another area that has received particular interest recently is the possible role of exogenous antigens, such as *Chlamydia psittaci*, in the pathogenesis of ocular adnexal MALT lymphomas. A possible association of both primary and secondary MALT lymphomas of the ocular adnexa with *C. psittaci* created much excitement initially [14]; however, other studies could not demonstrate this microorganism in relatively large cohorts [15,16]. Chanudet *et al.* [17**] suggest that there may be geographic variation in the distribution of this microorganism, and, consequently, possibly differences in its significance in the lymphomagenesis in ocular adnexal MALT lymphomas. The clinical relevance of this finding is considerable, as antimicrobials could be included in the armamentarium for treatment of these tumors.

Diffuse large B-cell lymphoma

Depending on which series is evaluated, DLBCLs represent either the second or third most frequent primary B-NHL subtype occurring in the ocular adnexa [7,18,19]. In addition they are the major subtype of primary intraocular lymphomas, but the most common subgroup of systemic lymphomas that secondarily infiltrate the eye (see below). The latter fact is not surprising considering that systemic DLBCL is one of the most common types of lymphoma in adults, accounting for approximately 30–40% of cases of NHL [1]. These tumors are heterogeneous in their morphology, antigenic profile and molecular genetic features (Table 1).

Recently, Alizadeh and associates [20] investigated the gene expression signatures of systemic DLBCLs using lymphochip complementary DNA microarrays and showed that overall survival after chemotherapy was significantly greater in patients with high gene expression levels, which are characteristic of normal germinal centre B cells. These results were confirmed by other groups [21,22] using both unsupervised and supervised statistical methods. Three biologically and clinically distinct subgroups of DLBCL have been identified, each with a specific gene expression signature: type 1 DLBCLs resemble germinal centre B cells (approximately 50% of cases); type 2 share features with activated B cells (approximately 30% of cases); and the third group is termed type 3 [20,21]. These findings suggest that the subgroups of DLBCL arise from different stages of normal B-cell development, perhaps representing distinct entities. To date, no expression profiling studies on ocular DLBCLs have been reported, and, therefore, it remains to be determined whether the ocular adnexal DLBCLs, as well as the primary or secondary intraocular DLBCLs, can be subdivided into one or more of the above-mentioned prognostic groups on the basis of their gene expression profile.

Follicular lymphoma

Follicular lymphoma is a neoplasm of follicle centre cells (centrocytes and centroblasts) that has at least a partially follicular pattern [1]. Areas of diffuse or even pure diffuse growth patterns can, however, occur (Table 1). In European studies, follicular lymphoma is the third most commonly occurring primary B-NHL in the ocular adnexa [7,18] but is the most common secondary lymphoid tumor of the ocular adnexa (see below).
## Table 1 Morphologic, immunophenotypic, molecular biologic, and clinical characteristics of the three lymphoma subtypes presented

| Lymphoma subtype | Morphology | Tumor cell immune profile | Molecular biologic changes | Cell of origin | Clinical characteristics |
|------------------|------------|---------------------------|---------------------------|----------------|-------------------------|
| **MALT lymphoma** | Expansive growth in the marginal zone | CD79a⁺, CD20⁺, CD43⁻/⁺, BCL-2⁻/⁺, IgM⁺, IgD⁻, CD10⁻, CD23⁻, CD5⁻, cyclin D₁⁻ | Clonal IgH and IgL rearrangements | 'Memory' B cell | 8% of all NHLs |
|                  | Heterogeneous cell population: centrocyte-like cells, monocytoid B cells, plasmacytoid cells, occasional blasts | Presence of FDCs in reactive secondary follicles | Mutations in V region of IgH gene | | Peak age, 65 years |
|                  | Possibly follicular colonization | Monotypic cytoplasmic Ig in 10% | t(11;18)(q21;q21) in 15–40% | | F > M |
|                  | Possibly lymphoepithelial lesions | | t(14;18)(q32;q21) in 10% | | Most common primary ocular adenalex lymphoma, but occurs less frequently as a secondary tumor |
|                  | Often multifocal growth | | t(1;14)(p22;q32) in 5% | | Tendency to recur; possible concurrent or subsequent involvement of other extranodal sites |
| **DLBCL**        | Diffuse growth pattern | CD79a⁺, CD20⁺, BCL-6⁻ (70% of cases), CD10⁻ (25–50%), IgM > IgG > IgA | Clonal IgH and IgL rearrangements | Mature germinal centre B cell or post-germinal centre B cell | 40% of extranodal NHLs |
| Morphologic variants: | | 50–75% of cases | Numerous mutations in V region of IgH gene | | Average age: 60–70 years |
| centroblastic, immunoblastic, centroimmunoblastic, anaplastic, T-cell rich | CD30⁻ in lymphoma with anaplastic morphology | Bcl-2 gene rearrangements | M:F = 1:1 | | Second most primary ocular adnexal lymphoma, but most common intraocular lymphoma (both primary and secondary tumors) |
|                  | Rarely CD5⁺ or CD23⁺ | No FDC-MW | C-myc gene rearrangements in 20–30% of cases | | Rapidly growing tumor |
|                  | Ki-67 nearly always >40% | | Extremely rare | | Aggressive clinical course |
| **Follicular lymphoma** | Usually follicular growth pattern with occasional diffuse areas; rarely purely diffuse | CD20⁺, CD10⁻, BCL-2⁻ (90%), BCL-6⁻, IgM (50%), IgG (50%) | Clonal IgH and IgL rearrangements | Germinal centre B cell | 40% of all NHLs in the US, 20–30% in Europe |
|                  | Mixture of centrocytes and centroblasts with dominance of former | CD43⁺ (95%), CD23⁺, CD5⁻ | Numerous mutations in V region of IgH gene | | 5th–6th decades of life |
|                  | Monomorphic GCs with loss of zonation | Dense follicular FDC-MW | of IgH gene with ongoing mutations (intrachromosomal diversity) and resulting in the expression of BCL-2 in neoplastic germinal centres | | M:F = 1:1 |
|                  | Minimal or no apoptosis in GC | Reduction in growth fraction in neoplastic GCs versus reactive GCs, particularly in BCL-2² cases | t(14;18)(q32;q21) in 70–95%, | | Most common secondary ocular adenalex lymphoma |
|                  | Usually no macrophages with tingible bodies | Often CD10⁻ B cells in the interfollicular region | p53 gene mutations and c-myc rearrangement in high-grade cases | | Lymph nodes mainly infiltrated, but also spleen, bone marrow, and skin |
|                  | Thin or even absence of the follicle mantle | Dense, well-defined FDC meshworks in neoplastic germinal centres (demonstrated with CD21) | Transformation to DLBCL in 30% of cases | | Often advanced disease at the time of diagnosis |

**MALT**, mucosa-associated lymphoid tissue lymphoma; Ig-H, immunoglobulin heavy chain; Ig-L, immunoglobulin light chain; NHL, non-Hodgkin lymphoma; F, female; M, male; FDC, follicular dendritic cell; DLBCL, diffuse large cell B-cell lymphoma; REL, reticuloendotheliosis oncogene; FDC-MW, follicular dendritic cell meshworks; GC, germinal centre.

* These results arise from investigations of NHLs in other locations.

* Rearrangements demonstrable in only 50–70% of cases due to presence of somatic mutations.
The vast majority of follicular lymphomas, including ocular adnexal follicular lymphoma, have cytogenetic abnormalities, the most common being t(14;18)(q32;q21), involving the rearrangement of the \( BCL-2 \) gene (70–95% of cases). Rare cases have a t(2;18)(p12;q21), which places the \( BCL-2 \) gene adjacent to the light chain on chromosome 2. Furthermore, most follicular lymphomas have additional breaks, most commonly involving chromosomes 1, 2, 4, 5, 13, and 17, or additions of X, 7, 12, or 18 [1]. Depending on the stage of the disease, most patients with ocular adnexal follicular lymphoma are treated using either radiotherapy (stage I and II) or chemotherapy (stage III and IV; secondary ocular adnexal follicular lymphoma). The latter, which encompasses a vast range of regimens, has been combined with radiotherapy and with anti-CD20 antibody therapy. The prognosis of follicular lymphoma has recently been demonstrated to be dependent on the tumor-infiltrating immune cells, such as macrophages [26]. To date, there is no curative treatment for advanced follicular lymphoma.

**Extraocular lymphomas: secondary tumors**

Secondary ocular adnexal lymphomas (S-OALs) develop in only a small proportion of patients with systemic lymphoma. Lazzarino et al. [27] reported that 2.4% of 325 patients with systemic NHL presented with orbital tumors, whereas Bairey et al. [28] found that 5.3% of 187 such patients had orbital or ocular adnexal involvement. Between 10 and 32% of all OALs are secondary [6,24,25,29].

The symptoms and signs of S-OALs are quite variable but are not significantly different from those of patients presenting with primary ocular adnexal lymphomas (P-OALs). It is, therefore, essential to determine disease stage in all patients with OAL prior to starting therapy, so that systemic disease is detected.

Interestingly, the prevalence of the lymphoma subtypes in S-OAL is quite different from that of the P-OALs. As mentioned above, most P-OALs are MALT lymphomas; these seldom develop as a secondary tumor [6,24]. In contrast, most secondary tumors are follicular lymphomas, which account for between 33 and 66% of all S-OALs in Western studies (Table 1) [6,23,24,25]. This is followed by (in approximate decreasing frequency) multiple myeloma/plasmacytoma [30–33]; lymphoplasmocytic lymphoma/immunocytoma (including Waldenström’s macroglobulinemia) [34,35]; mantle cell lymphoma, DLBCL, Burkitt lymphoma [36–38,39*], MALT lymphoma; and chronic lymphocytic leukemia [6,23,24,40*] (Fig. 1). Hodgkin’s lymphoma does not involve the ocular adnexa, except in advanced systemic disease [23*,41]. Initial presentation of Hodgkin’s lymphoma with ocular adnexal disease is extremely rare [42].

**Intraocular lymphoma**

Lymphomas occurring in intraocular structures can be divided into three main groups: primary intraocular lymphoma; primary uveal lymphoma; and secondary intraocular (uveal) lymphoma. The first two entities are mentioned very briefly before the secondary tumors are discussed. For detailed accounts of these tumors, the reader is referred to the respective articles on clinical, histopathological and treatment aspects of intraocular lymphoma.

**Primary retinal lymphoma**

Primary retinal lymphoma is generally referred to, imprecisely, as primary intraocular lymphoma. Briefly, this is a high-grade malignant B-cell lymphoma that affects the retinal pigment epithelium, sensory retina, vitreous, and optic nerve, usually sparing the uveal tract. Typically, it occurs in patients in the 6th or 7th decade of life (median age, 64 years) [43] with a female to male ratio of approximately 1:2:1. The ocular disease usually presents in isolation, but central nervous system (CNS) disease often develops before or subsequent to the ocular manifestations [9,44–47]. The combined manifestation of lymphoma in cerebral and ocular sites is referred to as oculocerebral lymphoma. Systemic dissemination of primary intraocular lymphoma is rare. Despite improvements in therapy [48,49], the prognosis in primary intraocular lymphoma is generally still poor.

**Primary uveal lymphoma**

Primary uveal lymphoma is a low-grade B-cell neoplasm of MALT type (see above), occurring usually unilaterally in men in the 5th or to 6th decades of life [50,51,52]. The prognosis for primary choroidal lymphoma is very good, with only exceptional cases of systemic dissemination or of CNS involvement [53,54].

**Secondary intraocular lymphoma**

Secondary intraocular lymphoma usually arises in the uvea, without involvement of the neurosensory retina [47,55,56]. Predominantly retinal disease without uveal infiltration has been reported but is exceptional [37,38*]. Rarely, systemic lymphoma can present with anterior segment disease such as pseudohypopyon or iridal infiltration [59–61]. Other unusual manifestations of secondary intraocular lymphoma include optic disk swelling [62], serous macular detachments [63*], and a lymphoma-associated retinopathy [64]. The exact incidence of secondary intraocular lymphoma is uncertain and probably will remain so as the number of autopsies performed decreases worldwide.

The most common systemic lymphoma subtype involving the eye is DLBCL (Table 1) [55,58*,59,65]. This is followed by multiple myeloma [66,67], lymphoplasmocytic lymphoma/immunocytoma (including Waldenström’s macroglobulinemia) [62,63*,64,67] (Fig. 2), marginal zone B-cell lymphoma [54], and chronic lymphatic leukemia.
Exceptionally rare but fascinating cases are those of intravascular lymphoma with secondary involvement of the eye [70,71*] (Fig. 3). Treatment is very much dependent on the extent of the disease, the type of malignant lymphoma, and comorbidities.

Morphologically, it may be difficult to determine whether an ocular DLBCL is a primary or secondary tumor. Retinal infiltration usually indicates primary intraocular lymphoma whereas uveal involvement suggests secondary disease; however, there are always exceptions to any rule [57,58*]. Coupland et al. [72*] have recently found that the expression of various immunoglobulin transcription factors in systemic DLBCL is very different from that of primary retinal and CNS lymphomas. Clonal analysis studies [73*,74,75*] with sequencing of the polymerase chain reaction products may indicate whether clonal proliferations have originated from the same tumor or from two distinct primary lymphomas.

**T or T/natural killer cell lymphoma**

Ocular lymphomas of non–B-cell type are rare and represent approximately 1–3% of all lymphoproliferative lesions in these sites [7,76*,77]. Most non–B-cell lymphomas are an extension of the tumor stage of mycosis fungoides or secondary manifestations of a systemic T-cell lymphoma [78*,79–92]. Primary T-cell lymphomas of the ocular adnexa are very rare, with less than 10 presumed cases being reported in the literature to date [77,93–97]. Similarly, primary intraocular lymphomas of T-cell type without involvement by mycosis fungoides are exceptional [98*,99–101].
Recent ophthalmic literature has described the rare primary and secondary involvement of the ocular tissues by T/natural killer cell lymphoma [93,102], adult T-cell lymphoma in conjunction with systemic leukemia, and associated with human T-cell lymphotropic virus type I infection [78,103–105]. All of these lymphoma entities are very aggressive, and patients usually die soon after initial diagnosis.

**Conclusion**

Much progress has been made in the understanding of malignant lymphomas in general. The WHO lymphoma classification has improved our ability to subtype the malignant lymphomas into particular entities, which are characterized by particular morphologic, immunophenotypical, and molecular biologic features. Further fine tuning of this comprehension of lymphomagenesis has been recently achieved with the application of the new technologies, e.g. complementary DNA microarrays. Much remains to be learned about the pathogenesis of the lymphomas affecting ocular and ocular adnexal tissues. The new methods must be applied in these tumors with the hope of optimizing patient treatment.

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**Figure 2 Intraocular manifestation of Waldenström’s macroglobulinemia**

(a) Minuscule biopsy material of an intraocular lymphomatous manifestation with positivity for (b) CD20 and (c) IgM.

**Figure 3 High-grade intravascular lymphoma**

Histologic section demonstrating a rare case of a high-grade intravascular lymphoma, which on immunophenotyping was demonstrated to be of B-cell origin. Courtesy of Dr H. Mudhar, Ophthalmic Pathology, Sheffield, Manchester, UK.
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