3 Ocular and Adnexal Lymphoma: Pathogenesis and Pathology

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Introduction

Ocular and adnexal lymphoma (OAL) refers to lymphoma involving either the orbit or the ocular adnexa. The ocular adnexa refers to tissues and structures surrounding the eye, such as conjunctiva, the lacrimal gland, the eyelids, and the surrounding orbital soft tissue. Approximately 8% of all extranodal lymphomas arise in the ocular adnexa [1]. Ocular adnexal lymphomas predominantly affect older individuals, with a median age in the 60s, and with a slight female predominance. Intraocular lymphomas are rare, representing less than 1% of all intraocular tumors and have a close association with primary central nervous system (CNS) lymphoma [2]. In this review, the histological and immunophenotypical features of the intraocular and ocular adnexal lymphomas will be discussed, and relevant molecular genetic features and pathogenesis will be briefly summarized.

Intraocular Lymphoma

Intraocular lymphoma is a subset of primary CNS lymphoma that may occur synchronously with lymphoma in the brain or is an isolated abnormality. Of all patients with primary CNS lymphoma, approximately 10–25% have ocular involvement. Patients with intraocular diffuse large B-cell lymphoma have a high risk of developing contralateral tumors (approximately 80%) or associated parenchymal central nervous system lesions [3]. Vitreoretinal lymphoma is another term used to refer to these high-grade intraocular malignancies. PCNSL-O is the preferred term to emphasize that it is an ocular variant or subset of primary CNS lymphoma (PCNSL).

To establish a diagnosis of lymphoma, patients may undergo vitrectomy, choroidal/retinal biopsy, or vitreous aspiration. In some cases, tailoring the biopsy approach in order to obtain fresh tissue for flow cytometry can be helpful to establish a clonal B-cell population [4]. The immunoglobulin genes are clonally rearranged and heavily somatically mutated, al1though demonstrating an immunoglobulin heavy chain or kappa region gene rearrangement is not a necessity for making the diagnosis [5, 6]. Determining the IL-10 and IL-6 levels in the vitreous may be helpful in evaluating the possibility of lymphoma since an elevated IL-10 level in the vitreous is strongly associated with ocular lymphoma. As a growth and differentiation factor for B cells, IL-10 promotes proliferation of neoplastic B cells and serves as an immunosuppressive cytokine that protects the lymphoma cells from the immune system. IL-6 may be released by the

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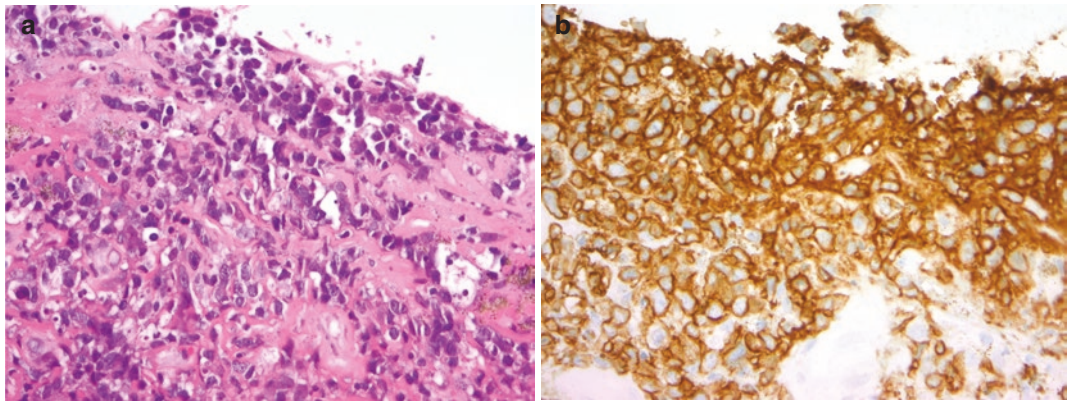

Fig. 3.1 Diffuse large B-cell lymphoma involving the choroid and retina. (**a**) There is a diffuse infiltrate of large neoplastic lymphocytes with irregular nuclear contours and hyperchromatic chromatin with occasional small nucleoli (400×, H&E). (**b**) The cells are diffusely positive for CD20 (400×, CD20)

reactive inflammatory population in cases of ocular lymphoma. An elevated IL-10 to IL-6 ratio suggests lymphoma rather than inflammation, but may not be elevated in early stages of lymphoma [6, 7].

Microscopically, the retina or optic nerve shows a diffuse perivascular infiltrate of large transformed lymphoid cells, with round or ovoid nuclei, nuclear membrane irregularities, high nuclear to cytoplasmic ratios, and prominent nucleoli (Fig. 3.1). Early in the course of disease, neoplastic cells can be found between Bruch's membrane and the retinal pigment epithelium [8]. Cytologic evaluation of the vitreous shows large pleomorphic lymphoid cells with nucleoli. Mitotic figures are easily identified. Necrosis and apoptosis with tingible body macrophages are present in highly proliferative lesions (Fig. 3.2).

The usual immunophenotype is characterized by positivity for B-cell antigens (CD20, CD79a, PAX 5), as well as positivity for MUM1, BCL2, BCL6, and usually monotypic IgM (Fig. 3.1). CD10 expression is much less common and could indicate secondary involvement by systemic diffuse large B-cell lymphoma. The tumors are Epstein-Barr virus negative. In immunocompetent patients, the histogenesis and immunophenotypic features correspond to the late germinal center or early post-germinal center stage of differentiation, quite similar to primary CNS lymphoma in the brain. Combining the non-germinal

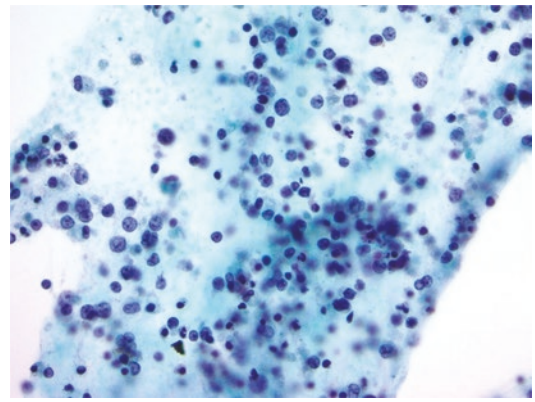

Fig. 3.2 Eye fine needle aspiration of vitreous showing an abnormal population of large lymphoid cells consistent with diffuse large B-cell lymphoma (400×, Thin-prep)

center immunophenotype (CD10−/BCL6+/−/MUM1+) by the Hans algorithm with the high somatic mutation load in the immunoglobulin variable region, this points to a histogenetic cell of origin corresponding to the activated B-cell-like subtype of diffuse large B-cell lymphoma by gene expression profiling [9–12].

Primary Uveal Lymphoma

Primary lymphoid proliferations of the uvea are rare and usually occur as primary choroidal lymphoma. Primary ciliary body lymphoma and pri-

mary iridal lymphoma are less common. Primary choroidal lymphoma was thought to be erroneously a form of reactive lymphoid hyperplasia in earlier literature, but subsequent study has shown that these have clinical and pathologic features of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue [13, 14]. Grossly, these lymphomas demonstrate diffuse thickening of the choroid that may result in retinal detachment. In some cases the overlying conjunctiva is involved, but overall changes occur slowly reflective of the indolent disease process [15].

Cytologic specimens will show a monotonous proliferation of small lymphocytes. Histologic biopsies show features of extranodal marginal zone lymphoma including a heterogeneous proliferation of centrocyte-like and monocytoid B cells, and occasional immunoblasts and plasmacytoid cells. Mitoses are infrequent. Lymphoepithelial lesions, or what has been described as the "uveal equivalent" can be seen as small lymphoma cells invading Bruch's membrane and the retinal epithelium [16]. Lymphoepithelial lesions are characteristic of marginal zone lymphomas of MALT type and are defined as aggregates of marginal zone B cells with distortion or distraction of the epithelium or glandular tissue [17]. Immunophenotypic studies demonstrate a light-chain restricted B-cell phenotype positive for CD20, CD79a, and PAX5 and usually negative for CD5, CD10, and cyclinD1 [16, 17].

Primary iridal lymphoma is extremely rare and demonstrates high-grade cytology. It is a cause of steroid-resistant uveitis in patients who usually have a history of an aggressive systemic B-cell lymphoma. Iris biopsies demonstrate sheets of large atypical transformed lymphocytes with pleomorphic cytology, frequent mitoses, and a high Ki-67 proliferative fraction [18]. In most cases, iridal involvement represents secondary iris infiltration by primary intraocular lymphoma, and the extent of iridal involvement is not documented until enucleation or post-mortem examination [19].

Secondary intraocular involvement by lymphoma involves spread to the eye by systemic lymphoma involving extranodal or lymph node primary sites. This usually arises by hematologic spread to the uvea and most commonly occurs as extension by primary CNS lymphoma, though many other systemic lymphomas have been reported including diffuse large B-cell lymphoma, some types of T-cell lymphoma, and lymphoblastic lymphomas [9].

Ocular Adnexal Lymphoma

Ocular adnexal lymphomas represent approximately 8% of extranodal lymphomas and are composed of several different subtypes. It is a disease of older adults with a slight female predominance. The prognosis largely depends upon the histologic diagnosis, with favorable outcomes in low-grade B-cell lesions such as extranodal marginal zone lymphoma (ENMZL) and follicular lymphoma [1]. Other subtypes of lymphoma known to occur in the ocular adnexa include mantle cell lymphoma (MCL), small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma (LPL), splenic marginal zone lymphoma (SMZL), diffuse large B-cell lymphoma, not otherwise specified, lymphoblastic lymphoma, peripheral T-cell lymphoma, and extranodal NK/T-cell lymphoma, nasal type. Classic Hodgkin lymphoma is exceedingly rare and occurs as a secondary manifestation. Marginal zone lymphoma usually involves the ocular adnexa as a primary site, with fewer cases of follicular lymphoma and diffuse large B-cell lymphoma arising as ocular adnexal primaries, and the other listed subtypes may involve the ocular adnexa secondarily [20]. Of patients with non-Hodgkin lymphoma, approximately 5% will develop secondary ocular adnexal involvement during the course of their disease [21]. This section describes the histologic, immunophenotypic, and genetic findings of some of the more common types of non-Hodgkin lymphoma involving the ocular adnexa.

Extranodal Marginal Zone Lymphoma (ENMZL) of Mucosa-Associated Lymphoid Tissue (MALT)

ENMZL was first described in the stomach but can arise in a variety of extranodal sites. These are indolent lymphomas that usually arise from mucosa-associated lymphoid tissue that accumulates as a result of a chronic inflammatory disorder, chronic antigenic stimulation, and/or autoimmunity. ENMZL is often referred to as "MALT" lymphomas when involving overlying epithelium such as conjunctiva or lacrimal gland acinar structures, but this designation is not appropriate when referring to marginal zone lymphomas involving areas deep within the orbit [22].

Histologic findings in ENMZL of the ocular adnexa include mass-forming infiltrates of small to medium-sized irregular lymphoplasmacytic infiltrates, residual foci of follicular center cells, and lymphoepithelial lesions in areas where there is overlying epithelium (Fig. 3.3a, b). There are rare to few mitoses. Dutcher bodies and polykaryocytes are sometimes identified [20]. One study of histologic characteristics showed that some features that are typical of ENMZL-MALT at other sites including monocytoid cytology, plasmacytoid differentiation, and lymphoepithelial lesions are less common in ENMZL affecting the ocular adnexa [23].

The immunophenotype of ENMZL is reflective of the histogenetic origin as marginal zone B cells (Fig. 3.3c). The lymphomas are positive for CD19, CD20, CD79a and often aberrantly express CD43 (a T-cell marker) and BCL2 (Fig. 3.3). There is restricted surface immunoglobulin expression that can be demonstrated by flow cytometry. CD21 positive follicular dendritic cell meshworks are sometimes expanded or disrupted by the infiltrate. Plasmacytic differentiation can be demonstrated by Dutcher bodies and immunoglobulin deposits and immunohistochemistry for kappa and lambda demonstrating

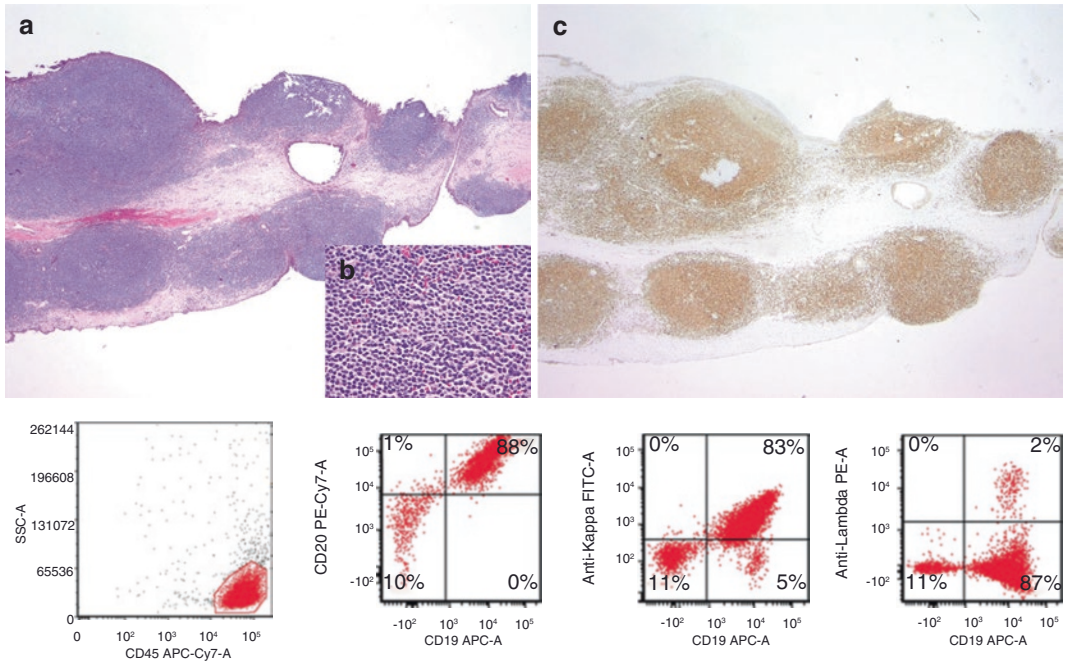

Fig. 3.3 Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue. (**a**) There are diffuse and nodular aggregates of lymphoma associated with the conjunctiva epithelium (10×, H&E). (**b**) The cells are monotonous with moderate cytoplasm and there is a circumscribed focus of larger cells toward the right edge of the photograph consistent with a residual follicle (400×, H&E). (**c**) The infiltrate is composed of excess B cells (400×, CD20). The lower row of images are flow cytometry plots. The analysis shows a uniform lymphoid population positive for CD19, CD20, and monotypic kappa surface immunoglobulin

monotypic cytoplasmic immunoglobulin [24] (Fig. 3.3). CD5 is rarely expressed, and cyclinD1 is negative. IRTA1 is a newer marker that was developed to assist in the differential diagnosis of marginal zone lymphomas. It is expressed by monocytoid B cells, marginal zone cells, and intraepithelial B cells in normal tissues and was demonstrated to be a helpful, specific marker in identification of ENMZL when present, though has limited sensitivity [25].

Flow cytometry or molecular methods are essential in the differential diagnosis of ENMZL from reactive lymphoid hyperplasia. Earlier studies of lymphoproliferative lesions identified histologic criteria to separate reactive lymphoid hyperplasia at one end of the histologic spectrum from other B-cell lymphoma types, but demonstrating a clonal population by light chain restriction or PCR is optimal for diagnosis [24]. Immunoglobulin heavy-chain and light-chain genes are clonally rearranged and can be demonstrated with testing using BIOMED-2/EuroClonality consensus primer sets, which detect a clonal population in approximately 85% of cases [26].

In order for flow cytometry to be performed, biopsies must be of sufficient size to allow for morphologic review and to allow for a single cell suspension to be derived from processing of fresh tissue. A portion of the specimen must be sent fresh or in supportive media to the performing laboratory within time requirements for stability. If flow cytometry is not performed, it can be difficult to detect light chains in neoplastic lymphocytes using tissue sections alone. However, recent data employing newer techniques for ultrasensitive detection of kappa and lambda using a RNA-based in situ hybridization method has shown results comparable or superior to flow cytometry. In a study of tissue biopsies fixed in formalin, RNA in situ hybridization identified light-chain restricted B cells in 89% of B-cell lymphomas compared to 67% of B-cell lymphomas by flow cytometry [27].

Several genetic abnormalities have been described in ENMZL/MALT lymphoma, including trisomy of chromosome 3 and chromosome 18 in slightly over half of cases. Gains of chromosome 3 are found more frequently in orbital cases compared with lymphomas involving the lacrimal gland [23, 28]. Recurrent translocations include t(11;18)(q21;q21)/*BIRC3::MALT1*, t(1;14)(p22;q32)/*BCL10::IGH*, t(14;18)(q32;q21)/*IGH::MALT1*, and t(3;14)(p13;q32)/*FOXP1::IGH* [29–31]. The oncogenic products of the first three translocations cause NF-κB activation. In MALT lymphomas lacking the above translocations, array comparative hybridization identified that the A20 gene, an inhibitor of NF-κB activity, was inactivated by somatic deletion or mutation in ocular adnexal ENMZL [32]. Details of recurrent chromosomal abnormalities in ENMZL are found in Table 3.1.

Table 3.1 Cytogenetic and molecular genetic abnormalities in ocular adnexal extranodal marginal zone lymphoma

Structural abnormality	Genes involved	Frequency (%)
+3		38%
+18		13%
t(11;18)(q21;q21)	*BIRC3*, *MALT1*	0–10%
t(14;18)(p14;q32)	*IGH*, *MALT1*	7–25%
t(3;14)(p22;q32)	*IGH*, *FOXP1*	0–20%

Pathogenesis and Etiology

ENMZLs arise in lymphoid tissue in extranodal sites as a result of chronic inflammation due to antigen stimulation and sometimes autoimmune disorders. For example, there is strong evidence that gastric MALT lymphoma and infection with *Helicobacter pylori* are closely linked. The significance of *C. psittaci* infection to development of ENMZL of the ocular adnexa is still unclear. In 2004, a high association between this organism and conjunctival MALT lymphoma was demonstrated by PCR studies. Furthermore, eradication of infection with doxycycline was effective in treating the lymphoma and producing a complete response [33]. This group went on to culture *C. psittaci* in blood and conjunctiva from patients with OAL and demonstrated its absence in normal healthy controls [33]. However, subsequent studies from other groups worldwide have

demonstrated significant variability in association with *C. psittaci* between regions of the world and between studies and variable efficacy of antibiotics as treatment. In general, higher prevalence rates in Italy and South Korea have been described, with a lower incidence in the USA. Lack of *C. psittaci* in some series indicates that geographic heterogeneity may be a contributing factor to differences in pathogenesis of ENMZL [23, 34].

Other Subtypes of Ocular Adnexal Lymphoma

Diffuse large B-cell lymphoma and related large B-cell lymphomas are aggressive tumors composed of transformed cells, either derived from centroblasts (germinal center like-cells) or activated B-cell-like cells committed to terminal B-cell differentiation stages [11]. Some lymphomas in this category have high-grade cytology with intermediate-sized or blastoid nuclei. These may secondarily involve the ocular adnexa and form destructive masses, but it is sometimes difficult to determine if these lymphomas arise from the orbit primarily [20]. Diffuse large B-cell lymphoma is a heterogeneous disease with many biologic factors and oncogenic mechanisms that impact response to therapy and survival, and pathologic evaluation involves, at a minimum, histologic review, cell of origin classification by immunohistochemistry, and FISH studies for additional classification and prognostication [35].

Follicular lymphoma is the second most common indolent B-cell lymphoma occurring in the ocular adnexa [20]. It is a neoplasm of malignant centrocytes and centroblasts, which are derived from the germinal center. The growth pattern can be follicular or partially follicular, but purely diffuse low-grade patterns are also recognized. Grading according to the proportion of centroblasts is used to further subclassify into categories of grade 1-2, 3A, and 3B recognized by the WHO classification. Follicular lymphoma has a distinctive immunophenotype involving expression of germinal center markers including CD10, BCL6, and MEF2B and demonstrates abnormal expression of BCL2 in most cases. The t(14;18)(q32;q21) is an early event in most cases, though translocation negative follicular lymphomas are also described. Additional genetic and epigenetic abnormalities are responsible for the pathogenesis [36].

Ocular adnexal mantle cell lymphoma more often represents secondary involvement of this region in patients with a history of mantle cell lymphoma in other extranodal sites such as the Waldeyer ring, gastrointestinal tract, and soft tissue [20]. The lymphoma is usually aggressive and presents at a high clinical stage, with frequent bilateral involvement and poor prognosis. The cells are small- to medium-sized with irregular or cleaved nuclei, and cytologically can mimic

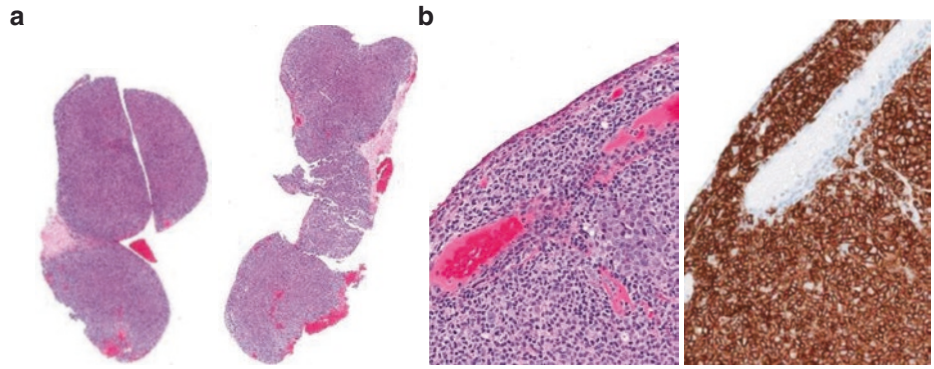

Fig. 3.4 Mantle cell lymphoma involving conjunctiva. (**a**) There are multiple nodular, expansive aggregates of lymphocytes under the epithelium (20×, H&E), composed of intermediate-sized monotonous lymphocytes with irregular nuclei (400×, inset). (**b**) The lymphocytes are positive for cyclinD1 by immunohistochemistry (20×, cyclinD1)

low-grade indolent B-cell lymphomas including MZL and follicular lymphoma (Fig. 3.4a). The lymphoma cells are positive for B-cell antigens and CD5, cyclinD1, and SOX11, with monoclonal surface immunoglobulin [37] (Fig. 3.4b).

Conclusions

Ocular and adnexal lymphomas are usually B-cell lymphomas that vary in histologic characteristics and behavior. The incidence of OAL has risen over the past several decades, increasing up to 6.5% per year according to SEER data [38]. Our understanding of lymphoma histology and biology and the molecular genetic underpinnings of the lymphoma subtypes has also grown relatively quickly in parallel, and additional studies to identify risk factors and additional pathogenetic mechanisms will be helpful for future prevention and therapy.

References

1. Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. Cancer. 1972;29(1):252–60.
2. Bardenstein DS. Intraocular lymphoma. Cancer Control. 1998;5(4):317–25.
3. Korfel A, Schlegel U. Diagnosis and treatment of primary CNS lymphoma. Nat Rev Neurol. 2013;9(6):317–27.
4. Wilson DJ, Braziel R, Rosenbaum JT. Intraocular lymphoma. Immunopathologic analysis of vitreous biopsy specimens. Arch Ophthalmol. 1992;110(10):1455–8.
5. Coupland SE, Hummel M, Müller H-H, Stein H. Molecular analysis of immunoglobulin genes in primary intraocular lymphoma. Invest Ophthalmol Vis Sci. 2005;46(10):3507–14.
6. Chan C-C. Molecular pathology of primary intraocular lymphoma. Trans Am Ophthalmol Soc. 2003;101:275–92.
7. Whitcup SM, Stark-Vancs V, Wittes RE, Solomon D, Podgor MJ, Nussenblatt RB, et al. Association of interleukin 10 in the vitreous and cerebrospinal fluid and primary central nervous system lymphoma. Arch Ophthalmol. 1997;115(9):1157–60.
8. Commins DL. Pathology of primary central nervous system lymphoma. Neurosurg Focus. 2006;21(5):E2.
9. Salomão DR, Pulido JS, Johnston PB, Canal-Fontcuberta I, Feldman AL. Vitreoretinal presentation of secondary large B-cell lymphoma in patients with systemic lymphoma. JAMA Ophthalmol. 2013;131(9):1151–8.
10. Grimm SA, McCannel CA, Omuro AMP, Ferreri AJM, Blay J-Y, Neuwelt EA, et al. Primary CNS lymphoma with intraocular involvement: International PCNSL Collaborative Group Report. Neurology. 2008;71(17):1355–60.
11. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000;403(6769):503–11.
12. Choi WWL, Weisenburger DD, Greiner TC, Piris MA, Banham AH, Delabie J, et al. A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy. Clin Cancer Res. 2009;15(17):5494–502.
13. Ryan SJ, Zimmerman LE, King FM. Reactive lymphoid hyperplasia. An unusual form of intraocular pseudotumor. Trans Am Acad Ophthalmol Otolaryngol. 1972;76(3):652–71.
14. Grossniklaus HE, Martin DF, Avery R, Shields JA, Shields CL, Kuo IC, et al. Uveal lymphoid infiltration. Report of four cases and clinicopathologic review. Ophthalmology. 1998;105(7):1265–73.
15. Knowles DM, Jakobiec FA, McNally L, Burke JS. Lymphoid hyperplasia and malignant lymphoma occurring in the ocular adnexa (orbit, conjunctiva, and eyelids): a prospective multiparametric analysis of 108 cases during 1977 to 1987. Hum Pathol. 1990;21(9):959–73.
16. Coupland SE, Damato B. Understanding intraocular lymphomas. Clin Exp Ophthalmol. 2008;36(6):564–78.
17. Cook JR, Isaacson PG, Chott A, Nakamura S, Muller-Hermelink HK, Harris NL, et al. Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: IARC; 2016. p. 259–65.
18. Mashayekhi A, Shields CL, Shields JA. Iris involvement by lymphoma: a review of 13 cases. Clin Exp Ophthalmol. 2013;41(1):19–26.
19. Velez G, de Smet MD, Whitcup SM, Robinson M, Nussenblatt RB, Chan CC. Iris involvement in primary intraocular lymphoma: report of two cases and review of the literature. Surv Ophthalmol. 2000;44(6):518–26.
20. Ferry JA, Fung CY, Zukerberg L, Lucarelli MJ, Hasserjian RP, Preffer FI, et al. Lymphoma of the ocular adnexa: a study of 353 cases. Am J Surg Pathol. 2007;31(2):170–84.
21. White WL, Ferry JA, Harris NL, Grove AS. Ocular adnexal lymphoma. A clinicopathologic study with identification of lymphomas of mucosa-associated lymphoid tissue type. Ophthalmology. 1995;102(12):1994–2006.
22. Harris NL, Isaacson PG. What are the criteria for distinguishing MALT from non-MALT lymphoma at

extranodal sites? Am J Clin Pathol. 1999;111(1 Suppl 1):S126–32.
23. Ruiz A, Reischl U, Swerdlow SH, Hartke M, Streubel B, Procop G, et al. Extranodal marginal zone B-cell lymphomas of the ocular adnexa: multiparameter analysis of 34 cases including interphase molecular cytogenetics and PCR for Chlamydia psittaci. Am J Surg Pathol. 2007;31(5):792–802.
24. Coupland SE, Krause L, Delecluse HJ, Anagnostopoulos I, Foss HD, Hummel M, et al. Lymphoproliferative lesions of the ocular adnexa. Analysis of 112 cases. Ophthalmology. 1998;105(8):1430–41.
25. Wang Z, Cook JR. IRTA1 and MNDA expression in marginal zone lymphoma: utility in differential diagnosis and implications for classification. Am J Clin Pathol. 2019;151(3):337–43.
26. Evans PS, Pott C, Groenen PJTA, Salles G, Davi F, Berger F, et al. Significantly improved PCR-based clonality testing in B-cell malignancies by use of multiple immunoglobulin gene targets. Report of the BIOMED-2 Concerted Action BHM4-CT98-3936. Leukemia. 2007;21(2):207–14.
27. Guo L, Wang Z, Anderson CM, Doolittle E, Kernag S, Cotta CV, et al. Ultrasensitive automated RNA in situ hybridization for kappa and lambda light chain mRNA detects B-cell clonality in tissue biopsies with performance comparable or superior to flow cytometry. Mod Pathol. 2018;31(3):385–94.
28. Remstein ED, Dogan A, Einerson RR, Paternoster SF, Fink SR, Law M, et al. The incidence and anatomic site specificity of chromosomal translocations in primary extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) in North America. Am J Surg Pathol. 2006;30(12):1546–53.
29. Streubel B, Lamprecht A, Dierlamm J, Cerroni L, Stolte M, Ott G, et al. T(14;18)(q32;q21) involving IGH and MALT1 is a frequent chromosomal aberration in MALT lymphoma. Blood. 2003;101(6):2335–9.
30. Akagi T, Motegi M, Tamura A, Suzuki R, Hosokawa Y, Suzuki H, et al. A novel gene, MALT1 at 18q21, is involved in t(11;18) (q21;q21) found in low-grade B-cell lymphoma of mucosa-associated lymphoid tissue. Oncogene. 1999;18(42):5785–94.
31. Willis TG, Jadayel DM, Du MQ, Peng H, Perry AR, Abdul-Rauf M, et al. Bcl10 is involved in t(1;14) (p22;q32) of MALT B cell lymphoma and mutated in multiple tumor types. Cell. 1999;96(1):35–45.
32. Chanudet E, Huang Y, Ichimura K, Dong G, Hamoudi RA, Radford J, et al. A20 is targeted by promoter methylation, deletion and inactivating mutation in MALT lymphoma. Leukemia. 2010;24(2):483–7.
33. Ferreri AJM, Dolcetti R, Dognini GP, Malabarba L, Vicari N, Pasini E, et al. Chlamydophila psittaci is viable and infectious in the conjunctiva and peripheral blood of patients with ocular adnexal lymphoma: results of a single-center prospective case–control study. Int J Cancer. 2008;123(5):1089–93.
34. Decaudin D, Dolcetti R, de Cremoux P, Ponzoni M, Vincent-Salomon A, Doglioni C, et al. Variable association between Chlamydophila psittaci infection and ocular adnexal lymphomas: methodological biases or true geographical variations? Anti-Cancer Drugs. 2008;19(8):761–5.
35. Sehn LH, Salles G. Diffuse large B-cell lymphoma. N Engl J Med. 2021;384(9):842–58.
36. Khanlari M, Chapman JR. Follicular lymphoma: updates for pathologists. J Pathol Transl Med. 2022;56(1):1–15.
37. Knudsen MKH, Rasmussen PK, Coupland SE, Esmaeli B, Finger PT, Graue GF, et al. Clinicopathological features of ocular adnexal mantle-cell lymphoma in an international multicenter cohort. JAMA Ophthalmol. 2017;135(12):1367–74.
38. Moslehi R, Devesa SS, Schairer C, Fraumeni JF. Rapidly increasing incidence of ocular non-Hodgkin lymphoma. J Natl Cancer Inst. 2006;98(13):936–9.