An update of ocular adnexal lymphomas

Robert M Verdijk

Abstract

The ocular adnexa (OA) include the eyelids, conjunctiva, lacrimal apparatus, and orbital soft tissue. One percent of all lymphomas and approximately 8% of all extranodal lymphomas arise in the OA and the incidence is increasing. The relative frequencies of ocular adnexal lymphoma presentation are orbit, 38%, conjunctiva, 31%, lacrimal apparatus, 18% and eyelid, 13%. The most frequent primary lymphoma types of the ocular adnexa are extranodal marginal zone lymphoma, 63%, follicular lymphoma, 16%, diffuse large B cell lymphoma 10%. The eyelids show the highest proportion of secondary lymphoma involvement, 47% of all eyelid lymphoproliferative lesions, compared with 20% in the other ocular adnexa. The specific aspects of the site, histologic, immunohistochemical, cytogenetic and molecular findings of the most relevant lymphoma types occurring in the various parts of the ocular adnexa will be discussed in relation to clinical parameters and relevance for therapy choice.

Keywords conjunctiva; cytogenetic analysis; diagnostic molecular pathology; epidemiology; eyelid; histopathology; immunohistochemistry; lacrimal apparatus; lymphoma; orbit

Introduction

The ocular adnexa (OA), the structures and tissues surrounding the eye, include the eyelids, conjunctiva, lacrimal apparatus, and orbital soft tissue. Theoretically any lymphoma can involve the OA. Malignant lymphomas are classified according to the presumed cell of origin as defined by the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues.[1] They can be divided into two major groups: Hodgkin lymphoma and non-Hodgkin lymphoma (NHL). Since Hodgkin disease of the OA is extremely rare this will not be discussed here. Primary ocular adnexal lymphoma (OAL) is defined as a lymphoma of the OA without evidence of concurrent systemic lymphoma and no prior history of lymphoma. Primary OAL should be staged according to the TNM classification devised for OAL (Table 1) since the TNM-based staging system better predicts outcome in OAL than the Ann Arbor system.[2]

The specific aspects of the site, the frequency and various types of lymphoma occurring in the various parts of the OA will be discussed. This review will continue to describe the most common OAL types and discuss the specific aspects in relation to systemic lymphoma or lymphoma at other sites, molecular and cytogenetic alterations, treatment options and outcome.

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Regional peculiarities

The orbital bone and (peri-) ocular connective tissues are derived from neural crest cells, i.e. mesectoderm not mesoderm. The lacrimal gland arises from a thickening of the ectoderm of the superior conjunctival fornix, the mesenchymal cells that surround the point of epithelial budding are of neural crest origin. Although not much attention has been directed at this peculiar aspect of the OA region this exceptional mesenchymal environment can be expected to be of relevance to the specific aetiologic, molecular genetic and clinical features of OAL.

In the non-diseased lacrimal gland IgA producing plasma cells account for approximately 50% of all lymphoid cells. T cells, representing the second most common cell type, are located predominantly in lymphocytic foci and singly in the interstitium of the lacrimal gland. Conjunctival lymphoid tissue can be observed in the healthy palpebral conjunctiva, more pronounced in the upper than in the lower lid. It occurs both as diffuse lymphocytes and IgA producing plasma cells located in the substantia propria. Additionally approximately 60% of non-diseased conjunctival sacs have organized lymphoid accumulations in the substantia propria. The epithelium of the lacrimal gland tubules and acini, as well as of the conjunctival crypts expresses lysozyme and the IgA secretory component. The conjunctiva and lacrimal gland thus belong to the mucosa-associated lymphoid system (MALT), also called eye-associated lymphoid tissue (EALT). Lymphocytes recirculate to the EALT via high endothelial venules (inflow) and lymph vessels (outflow). The non-conjunctival side of the eyelids contains disperse inflammatory cells, mainly CD4 positive T cells, macrophages and dendritic cells of the skin. The skin of the eyelids contain lymph vessels, comparable to skin at other sites. In contrast to the eyelid, conjunctiva and lacrimal gland, the soft tissues of the orbit and its contents are considered an extralymphatic site that does not contain lymph vessels nor lymphoid cells in a healthy state. This feature may relate to the ectomesenchymal derivation of these tissues in analogy to the brain and eye which are also without lymphatics.

Epidemiology

OA lymphoproliferative lesions includes benign and malignant disease such as lymphoid hyperplasia (LH)[3] and lymphoma based on histopathologic, immunophenotypic and molecular features. OAL represents malignant lymphoid neoplasms, which can develop as primary or secondary tumour manifestations. One percent to 2% of all lymphomas and approximately 8% of all extranodal lymphomas arise in the OA and the incidence is increasing.[4] In Europe there is a consistent overall increase in incidence of NHL. An estimated 5% of NHL patients develop secondary OA involvement during the course of their disease. Lymphoid tumours comprise 10% to more than 20% of orbital mass lesions in different series, and lymphoma is the most common orbital malignancy. Likewise, lymphomas involving the conjunctiva are relatively common. OAL is primarily a disease of older adults (peak age 65 years) with a slight female preponderance.

In order to gain insight into the relative frequencies of the types and location of OA lymphoid disease the diagnoses and location of 226 lymphoproliferative lesions from the past 27

TNM staging system for OAL

Primary tumour (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 Lymphoma with orbital involvement ± any conjunctival involvement
- T2a Anterior orbital involvement but no lacrimal grand involvement ± conjunctival disease
- T2b Anterior orbital involvement with lacrimal gland involvement ± conjunctival disease
- T2c Posterior orbital involvement ± conjunctival involvement ± any extraocular muscle involvement
- T2d Nasolacrimal drainage system involvement ± conjunctival involvement but not including nasopharynx
- T3 Lymphoma with preseptal eyelid involvement ± orbital involvement ± any conjunctival involvement
- T4 Orbital adnexal lymphoma extending beyond orbit to adjacent structures, such as bone and brain
- T4a Involvement of nasopharynx
- T4b Osseous involvement (including periosteum)
- T4c Involvement of maxillofacial, ethmoidal, frontal 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

Distal metastasis (M)

- MX Dissemination of lymphoma not assessed
- M0 No evidence of involvement of other extranodal sites
- M1 Lymphomatous involvement in other organs recorded either at first diagnosis or subsequently
- M1a Noncontiguous involvement of tissues or organs external to the ocular adnexa (e.g., parotid gland, submandibular gland, lung, liver, spleen, kidney, breast)
- M1b Lymphomatous involvement of the bone marrow
- M1c Both M1 and M1b involvement

Table 1

years in the department of Pathology of the Erasmus University Medical center were evaluated (Table 2). In this series the most frequent OA presentation is in the orbit 38%, followed by conjunctiva, 31%, lacrimal apparatus, 18% (only three cases involved the lacrimal sac), and eyelid 13%. LH is diagnosed in about 15% of cases, and is most common in the lacrimal gland (41% of all primary lymphoid lesions of the lacrimal gland, Table 2). The diagnosis LH is made based on morphology (Figure 1a) in the absence of a monoclonal population either by immunohistochemistry (Figure 1b–f) or flow cytometry and molecular techniques. It is widely recognized that the generally hypocellular lymphoid cell-poor orbital pseudotumors (idiopathic orbital inflammation) and LH represent distinct entities.[3] LH comprises 2% of all lesions of the orbit representing 7% of all inflammatory lesions.[5] There has been a shift in diagnostic patterns, with previously thought benign LH being reclassified as extranodal marginal zone lymphomas (ENMZL).[3]The most frequent primary OAL diagnosis is ENMZL in 44% of all lymphoid lesions and 63% of all primary OAL (Table 2). The highest frequency of ENMZL/MALT lymphoma is observed in the conjunctiva in 71% of all primary lymphoid conjunctival lesions. Primary marginal zone lymphomas of the orbit (48%) should be designated ENMZL, since no MALT tissue is supposedly involved in the genesis of these lesions. One case of gastric MALT lymphoma secondarily involved the orbit, but also the conjunctiva and lacrimal gland may show secondary involvement of distant MALT lymphoma (Table 2).[6] The different OA structures show a distinctly different disease spectrum. The eyelids show the highest proportion of secondary lymphoma involvement (47% of all eyelid lymphoproliferative lesions), and this probably also explains the most varied list of 12 different diagnostic entities, including T-cell lymphoma (Table 2). This seems to separate eyelid lymphoid lesions clearly from the other ocular adnexa. For the conjunctiva, lacrimal apparatus and orbit there is about 80% primary lymphoid lesions and 20% secondary involvement (Table 2).[6]

The second most frequent primary OAL diagnosis is follicular lymphoma (FL), 16% of all OAL, closely followed by diffuse large B cell lymphoma (DLBCL), 10%. Mantle cell lymphoma was diagnosed in 4% of primary lesions. Other primary