Original Article

Ocular adnexal lymphoproliferative disease: a series of 73 cases

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ABSTRACT

Background: This study involved 73 patients with lymphoproliferative lesions of the ocular adnexa. The lesions were categorized using the Revised European American Lymphoma classification of lymphoid tissues and analysed to determine the frequency and prognostic impact of tumour type, location, stage and patient's age and sex.

Methods: The clinical, histopathological, immunohistochemical and phenotypic analysis by flow cytometry and follow-up data were studied.

Results: The ocular adnexal lymphoproliferative lesions included 70 lymphomas and six reactive lymphoid hyperplasia. Seventy-nine per cent had stage IE disease, 4% stage II, 1.5% stage III and 15.5% stage IV. Five patients (7%) had a past history of systemic lymphoma. Major histological types were extranodal marginal zone lymphoma (MZL) in 44 (63%), follicular (FL) in 12 (17%), diffuse large B-cell (DLBCL) in eight (11%), mantle cell (MCL) in two (3%), B-cell chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma in two (3%), peripheral T-cell lymphoma (PTCL) one (1.5%) and natural killer cell lymphoma (NKCL) in one (1.5%). Longest survival was seen in those with low-grade lymphomas (MZL and FL) and worst in PTCL and NKCL. Lymphoma-related mortality was 2% for MZL, 33% for FL, 38% for DLBCL, and 100% for MCL, PTCL and NKCL. Systemic lymphoma was present prior to, at presentation or at subsequent follow up in 26/68 (39%) of all lymphoma patients, 17% for MZL, 38% for DLBCL, 83% for FL, and 100% for MCL, CLL, PTCL and NKCL.

Conclusion: The majority of ocular adnexal lymphomas were low-grade B-cell lymphomas (MZL). Multivariate analysis showed that the only significant independent predictors of all causes of mortality were the histological type of lymphoma and the stage of disease at presentation.

Key words: lymphoma, lymphoproliferative disorder, marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type, ocular adnexa, orbit.

INTRODUCTION

Lymphoproliferative lesions of the ocular adnexa (conjunctiva, eyelids and orbit) may present with symptoms of conjunctival salmon patches, ptosis from eyelid involvement or the insidious and painless development of proptosis and/or diplopia due to an orbital mass. Clinical and radiological features do not allow distinction of benign hyperplasias from malignant lymphoma, and tissue is ultimately required for histological diagnosis. Malignant lymphoma of the ocular adnexa can be a primary extranodal lymphoma, that is not associated with any systemic evidence of lymphoma, or secondary, with prior or concurrent extraocular lymphoma usually involving lymph nodes. Previous studies have demonstrated that with sufficiently long follow up, between one-third to one-half of the patients with ocular adnexal lymphoma develop systemic lymphoma.[1,2] It has been recognized that the majority of the primary ocular adnexal lymphomas are low-grade tumours, with features of extranodal marginal zone lymphoma (MZL).[2–5] These tumours are generally localized (stage IE) at presentation, respond well to local radiotherapy or oral chemotherapy, and have a favourable outcome.

Classification schemes of lymphomas have evolved with time from those based on morphology alone such as the Working Formulation[6] to the most recent proposed World Health Organization Classification[7] and its precursor, Revised European American Lymphoma Classification

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(REAL), which incorporate clinical features and ancillary laboratory investigations such as immunophenotyping and genotyping in addition to the histopathological findings.[7–9] Recent reports of ocular adnexal lymphomas[3,4] demonstrated that this classification scheme was useful in prediction of stage of disease at diagnosis, persistence of disease at final follow up and lymphoma-related death. We present our experience of 73 lymphoproliferative lesions, using the REAL classification and with clinical follow up of median 42 months (mean 47 months).

METHODS

Tissue samples

This series included cases of biopsy-proven lymphoproliferative lesions of the ocular adnexa derived from two major sources: 35 cases from the private practices of three of the authors (AMcN, ICF, JO'D) and 38 cases diagnosed at the Anatomical Pathology laboratory at St Vincent's Hospital, Melbourne, between January 1985 and December 1998. This series excluded any cases with lymphoproliferative lesions involving choroid, retina or vitreous (one patient with an episcleral nodule had concurrent choroidal disease and was not included in this series). The histopathology of the 35 external cases was reviewed by one of the authors (PMcK). The cases were classified according to the REAL classification of lymphomas using a combination of clinical, histological and immunohistochemical features.[6–8]

Immunocytochemistry was performed using a panel of antibodies including monoclonal antibodies CD20, CD79a, bcl-2, CD43, UCHL-1, kappa light chain, lambda light chain, CD5, cyclin D1 (selected cases) and polyclonal CD3. Detection kit used was DAKO LSAB2 System peroxidase kit (code No K0675; Dako, Glostrup, Denmark).

Phenotyping by flow cytometric analysis was performed using standard techniques and antibodies tested included CD45, CD14, CD5, CD19, CD3/CD4, CD3/CD8, IgG1, CD23, CD10, CD22, CD20, CD8, CD4, CD3, CD19, and Kappa and Lambda light chains.

Medical history

Clinical data was obtained including patient age, sex, medical history, clinical findings, anatomical location of the lesion, laboratory and radiological investigations, stage of disease at diagnosis (Ann Arbor Staging Classification modified for extranodal disease), type and extent of therapy, disease course, disease-free period, duration of survival and stage of disease at last follow up.[10] Patients with only bilateral ocular adnexal disease were considered to have stage IE disease. The anatomical localization was defined as proposed by previous authors.[1] Patients were staged with the use of various investigations including full clinical examination, computed tomography chest and abdomen, chest X-ray, full blood examination, serum electrophoresis and bone marrow examination.

Statistical analysis

Actuarial survival curves were plotted using the Kaplan–Meier method with a Stata (Stata Corporation, College Station, TX, USA).[11] Multivariate analyses were performed using a Cox proportional hazards model.[12] Three models using all cause mortality, all cancer mortality and lymphoma mortality for outcome were tested. In each case, the potential explanatory variables or predictors were histological subtype of lymphoma, stage, side, sex, age, site, presence of systemic lymphoma and prior or subsequent ocular adnexal lymphoproliferative disease.

RESULTS

Clinical features and anatomical distribution

Patient demographics and outcome of patients with lymphoma are presented in Table 1. The overall patient group consisted of 41 women and 32 men with an age range from 19 to 87 years (median 65 years). Six patients in the series had a diagnosis of reactive lymphoid hyperplasia, three of whom later developed marginal zone lymphoma (MZL). Four involved orbit and two were localized to the lacrimal gland. The six patients were five men and one woman with age range 51–69 years (median 61 years). The 70 patients with lymphomas comprised 41 women and 29 men, median age 65 years. No patients were diagnosed as suffering from Sjögren's syndrome, Mikulicz syndrome or Wegener's granulomatosis.

The location of the 70 ocular adnexal lymphomas is listed in Table 2. Synchronous bilateral lesions were noted in nine patients with lymphoma (13% of lymphomas): four lacrimal gland, three orbit and two conjunctiva. Five patients (7%) had a known history of non-Hodgkin's lymphoma. These were one with B-cell chronic lymphocytic leukaemia (CLL), two with follicular lymphoma (FL), one with diffuse large B-cell lymphoma (DLBCL) and one with MZL; however, one patient with prior FL presented with stage IE disease in ocular adnexa.

Histology

Eighty-four biopsies from 73 patients were examined. These included tissue from ocular adnexa as well as lymph node, spleen and bone marrow; and lymph node and urinary bladder in patients who developed systemic disease. Sixteen of 70 patients (23%) with ocular adnexal lymphoma had secondary lymphoma and 77% were primary.

Major subtypes and stage of disease at diagnosis are indicated in Table 3. Anatomical distribution of the different subtypes of lymphoma is indicated in Table 4. One patient with FL developed recurrence in the brow after 12 months, with transformation to a higher-grade lymphoma: precursor B lymphoblastic lymphoma.

Table 1. Patient demographics and outcome for histological subtype of ocular adnexal lymphoma (REAL classification)

Demographic	MZL $n = 44$*	CLL $n = 2$	FL $n = 12$	MCL $n = 2$	DLBCL $n = 8$	PTCL/NKCL $n = 2$	All $n = 70$*
Age at diagnosis (years) range (median)	19–87 (65)	62–65 (63.5)	50–80 (66)	64–80 (72)	28–76 (65)	27–41 (34)	19–87 (65)
Sex (no. male)	16 (36%)	0 (0%)	8 (67%)	1 (50%)	3 (38%)	1 (50%)	29 (41%)
Systemic spread							
At diagnosis	4 (9%)	2 (100%)	2 (16%)	2 (100%)	3 (38%)	2 (100%)	15 (21%)
At any time	7 (17%)	2 (100%)	10 (83%)†	2 (100%)	3 (38%)	2 (100%)	26 (39%)
Time to spread (months) range (median)	24–76 (36)	–	12–97 (42)	–	–	–	12–97 (42)
Relapse							
Local relapse	2 (5%)	–	2 (16%)	–	2 (25%)	–	6 (9%)
Time to relapse (months) range (median)	24–138 (52)	–	24–59 (41.5)		17		17–138 (33)
Deaths							
All deaths	3 (7%)	1 (50%)	5 (42%)	2 (100%)	3 (38%)	2 (100%)	16 (24%)*
Lymphoma-related deaths	1 (2%)	0 (0%)	4 (33%)	2 (100%)	3 (38%)	2 (100%)	12 (18%)*
Time to death of lymphoma (months) range (median)	37	–	25–99 (32)	24–36 (30)	9–28 (15)	1.5–3 (2.2)	1.5–99 (26.5)
Follow-up period (months) range (median)	4–150 (50)	9–147 (78)	25–100 (41)	24–36 (30)	9–94 (26)	1.5–3 (2.2)	1.5–150 (41)
Treatment							
Excisional surgery	7	–	1	–	–	–	8
Radiotherapy	12	1	6	–	1	–	20
Chlorambucil	21	–	2	–	–	–	23
Systemic chemotherapy	2	–	4	1	3	2	12
Chemotherapy + XRT	0	1	3	1	5	–	10
Prednisone	1	–	–	–	–	–	1

MZL, marginal zone lymphoma; CLL, B-cell chronic lymphocytic leukaemia/small lymphocytic leukaemia; FL, follicular lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; PTCL/NKCL, peripheral T-cell lymphoma and natural killer cell lymphoma.

*Two patients with MZL were lost to follow up; †one patient with FL had past history of nodal disease but only orbital disease at presentation and follow up.

Table 2. Anatomical localization of ocular adnexal lymphomas in relation to disease stage

Anatomical localization	Stage IE $n = 55$	Stage IIE $n = 3$	Stage IIIE $n = 1$	Stage IV $n = 11$	Total no. patients (%) $n = 70$
Eyelid	4	–	–	–	4 (5.8)
Conjunctiva	12	–	–	–	12 (17.0)
Orbit (excluding lacrimal gland)	29*	1	–	8	38 (54.3)
Lacrimal gland	8	2	1	3	14 (20.0)
Lacrimal sac	2	–	–	–	2 (2.9)

*One stage IE patient had contiguous brain and orbital disease.

Table 3. Histological type of lymphoma (REAL classification) and stage at diagnosis

Histological type	Stage IE $n = 55$	Stage IIE $n = 3$	Stage IIIE $n = 1$	Stage IV $n = 11$	Total no. patients (%) $n = 70$
MZL	40	2	1	1	44 (63)
CLL	–	–	–	2	2 (3)
FL	10	–	–	2	12 (17)
MCL	–	1	–	1	2 (3)
DLBCL	5*	–	–	3	8 (11)
PTCL/NKCL	–	–	–	2	2 (3)

*One stage IE patient had contiguous brain and orbital disease. For definitions see Table 1.

Table 4. Anatomical site of lymphoma versus histological type (REAL classification)

Anatomical site	MZL	CLL	FL	MCL	DLBCL	PTCL/ NKCL	Total
Eyelid	3	–	1	–	–	–	4
Conjunctiva	12	–	–	–	–	–	12
Orbit (excluding lacrimal gland)	21	1	8	1	5	2	38
Lacrimal gland	8	1	3	1	1	–	14
Lacrimal sac	–	–	–	–	2	–	2
Total no. patients	44	2	12	2	8	2	70

*One stage IE patient had contiguous brain and orbital disease. For definitions see Table 1.

Flow cytometry

This was performed in 20 cases of ocular adnexal tissue and results were contributory to the diagnosis of lymphoma or hyperplasia in 18. In one patient with orbital lymphoma, the initial biopsy was received in formalin and immunohistochemistry of the lymphoma was negative for all B and T markers. Flow cytometric analysis of fresh tissue from a second biopsy confirmed a natural killer cell lymphoma (NKCL) (CD2+ , CD3–, CD4–, CD7+ , CD8–, CD16/56+).

Clinical follow up

Of 73 patients, three were lost to follow up. The other 70 were followed for periods ranging from 1.5 months to 150 months (median 41 months, mean 47 months).

In three patients with lymphoid hyperplasia, MZL developed in the orbit after 33, 57 and 108 months (median 57 months; Fig. 1). Similar proportions have been reported by other authors with long follow up,[1,2] but not in studies with shorter follow up of 31 months.[3]

Treatment modalities, which are summarized in Table 1, included radiotherapy and/or systemic chemotherapy, comprising cyclophosphamide, vincristine and prednisone with or without doxorubicin. Oral chlorambucil was used in 19 patients with MZL.

Statistical analysis

Multivariate analyses were performed using a Cox proportional hazards model. A model using all cause mortality for outcome was tested. In each case, the potential explanatory variables or predictors were histological type of lymphoma, stage, side, sex, age, site (eyelid, conjunctiva, orbit, lacrimal gland and lacrimal sac), presence of systemic lymphoma, and prior or concurrent ocular adnexal lymphoproliferative disease. There were six categories of histological type (MZL, CLL, FL, mantle cell [MCL], DLBCL, and peripheral T-cell lymphoma [PTCL] and NKCL) for the purposes of analysis (Figs 1–3). Multivariate analysis showed that only the histological type of tumour (Fig. 4), stage of disease (Fig. 5) and presence of prior or concurrent systemic lymphoma (Fig. 6) were significant predictors of mortality ($P < 0.05$).

Kaplan–Meier survival curves plotted according to histological type of lymphoma (Fig. 4) showed best survival for the group of MZL, but due to survival of most patients, a 50% survival figure could not be calculated. Fifty per cent survival figures for other histological groups included CLL 147 months, FL 100 months, DLBCL 28 months, MCL 24 months and PTCL/NKCL 1.5 months.

Patient outcomes

Outcomes related to initial stage

Forty of 53 (75%) patients with stage IE disease and follow up were alive without developing systemic disease with a median follow up of 39 months.

Of 11 patients presenting with stage IV disease, seven died of lymphoma 1.5–36 months from time of diagnosis (median 15 months). One patient with stage IIIE MCL died of disseminated lymphoma at 24 months; however, the other three patients with stage II or III disease, all with MZL, were alive at median follow up of 58 months.

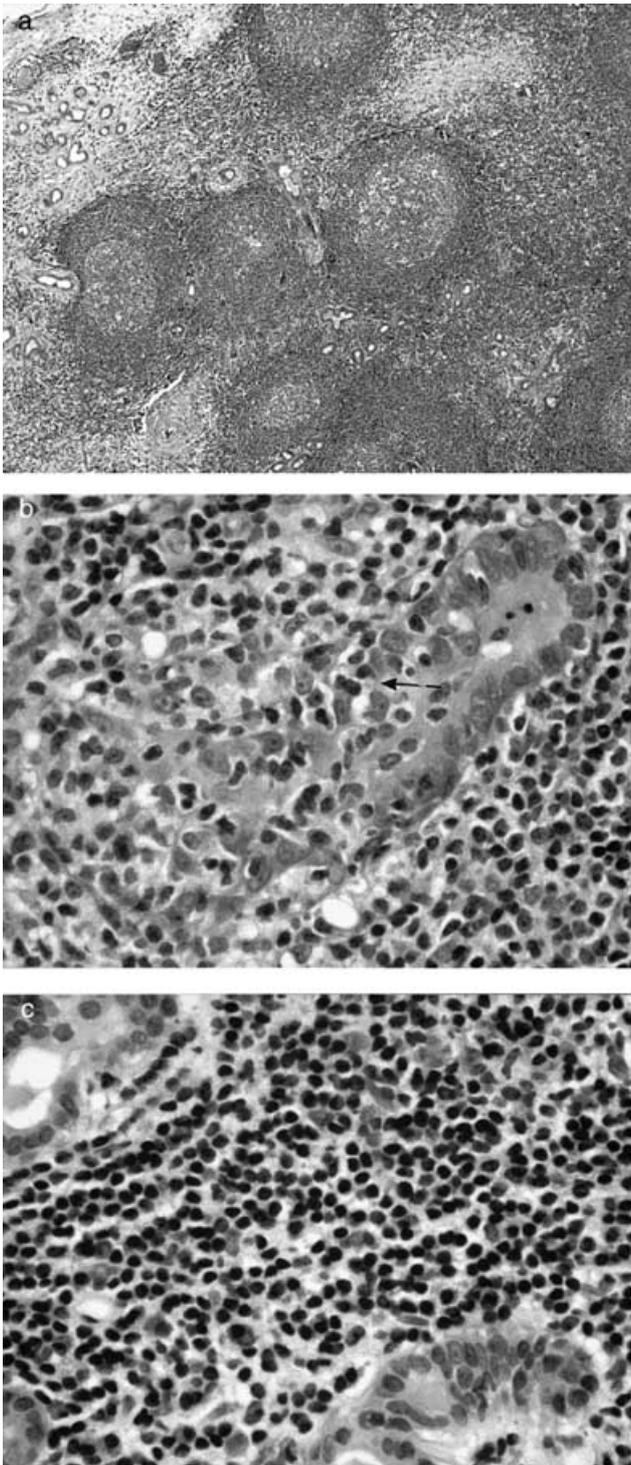### Development of extraocular or systemic disease

Data presented in Table 1 shows that 15 of 70 patients (21%) had systemic disease at presentation with the lowest incidence in the MZL group (only 9%). All of six patients with MCL, CLL and TCL/NKCL had systemic disease at diagnosis. Twenty-six of 68 patients with follow up (39%) had prior, concurrent or subsequent systemic lymphoma. The MZL group again had the lowest frequency of developing systemic disease (17%). Ocular adnexal lymphomas spread to lymph nodes, bone marrow, spleen, urinary bladder, pleural cavity, parotid glands, skin and subcutis. Local ocular adnexal relapse occurred in conjunctiva three times in one patient with MZL lymphoma (24–62 months).

Mortality

Data in Table 1 indicate that 16/68 (24%) lymphoma patients died; however, only 12 deaths were lymphoma-related (18%). Risk of lymphoma-related death was lowest for MZL (2%), moderate for FL (33%) and DLCL (38%) but highest in MCL, PTCL and NKCL (100%).
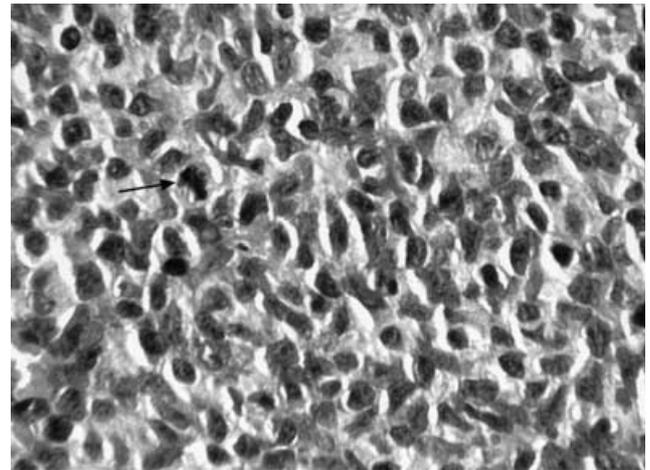
DISCUSSION

Large published series of ocular adnexal lymphoproliferative disease[1–5,13–16] have involved the use of different classifications

Figure 2. High-power view of follicular lymphoma with cleaved cells and mitotic figure (→). (H&E)

Figure 3. High-power view of diffuse large B-cell lymphoma with large blastic cells and mitotic figure (←). (H&E)
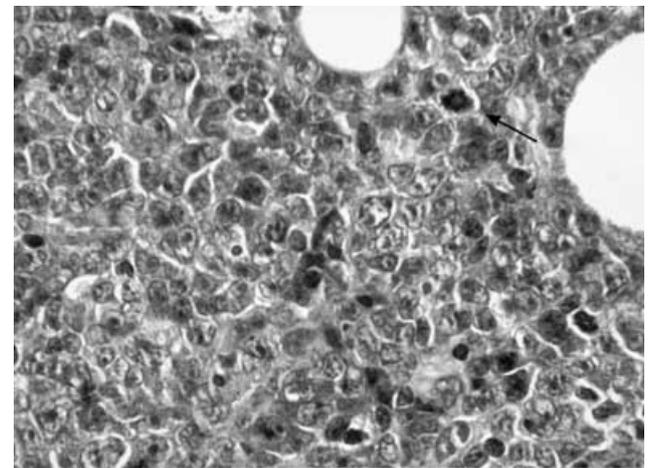
Figure 1. Marginal zone lymphoma of the lacrimal gland. (a) Low-power view of lymphoid follicles. (b) High-power view showing a lymphoepithelial lesion (←). (c) High-power view showing the population of lymphocytes, centrocyte-like cells and plasma cells. (H&E)
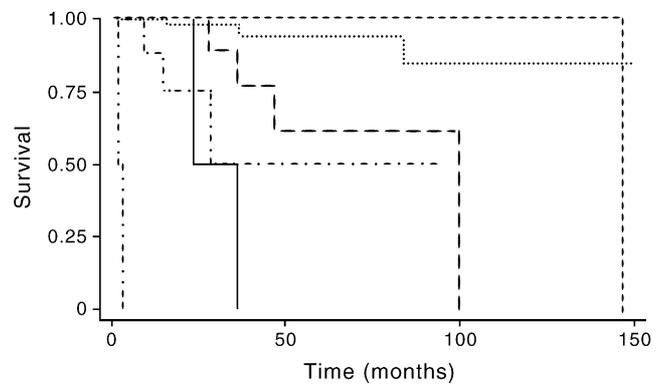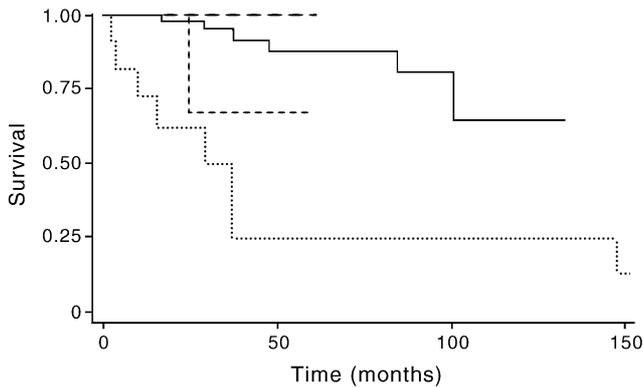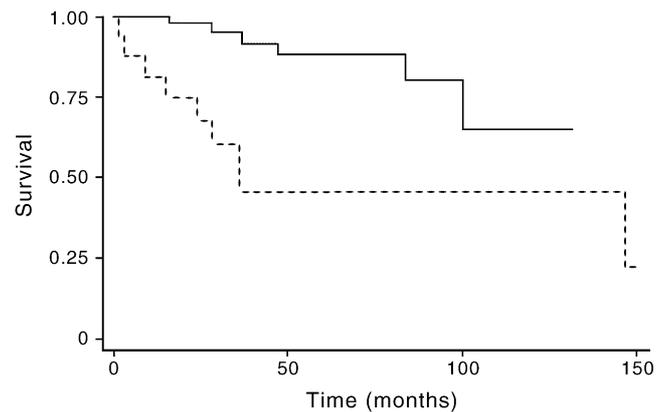

Figure 4. Kaplan–Meier survival curve for histological type of lymphoma. (…) Marginal zone lymphoma; (- - -) B-cell chronic lymphocytic leukaemia/small lymphocytic leukaemia; (– – –) follicular lymphoma; (—) mantle cell lymphoma; (– · –) large B-cell lymphoma; (· · · -) peripheral T-cell lymphoma and natural killer cell lymphoma.

of lymphomas: the Working Formulation,[1,6,14–16] the Working Formulation with addition of MZL and MCL,[2] and more recently the REAL Classification.[3,4,13] This means that

Figure 5. Kaplan–Meier survival curve for stage of disease. (—) Stage 1; (- - -) stage 2; (– – –) stage 3; (…) stage 4.

Figure 6. Kaplan–Meier survival curve for presence of systemic disease. (—) No systemic disease; (- - -) systemic disease.

there is some difficulty in direct comparison of the different studies, especially since the REAL classification has included recognition of new entities that were not present in the Working Formulation, such as MZL and MCL.[17–20]

Our study demonstrated several points. Ocular adnexal lymphomas are usually low-grade lymphomas (63% MZL), that occur as localized stage IE disease (91% in our series) in elderly patients (median age 65 years) with female preponderance. Marginal zone lymphoma responded well to either oral chemotherapy with chlorambucil or localized radiotherapy. Although relapse may occur locally, extranodally or with regional lymph node involvement (a further 8% developed extraocular disease), the recurrent lesions almost always responded to therapy. Only a small percentage (2%) of patients in our series with MZL died of disseminated lymphoma. These findings differ from those of a recent large study of 192 cases from Jenkins *et al.*, who reported 13% lymphoma-related death (11/82) and a 40% incidence of systemic disease for their group of patients with MZL.[4]

The important predictors of mortality in our series were histological type of lymphoma, stage of disease at presentation, and presence of prior or concurrent systemic lymphoma. The REAL classification of lymphomas allows prediction of clinical behaviour including risk of systemic disease and lymphoma-related death.[3,4] Prognosis is best for MZL with a 17% risk of systemic disease and a 2% mortality rate due to lymphoma. Patients with low grade lymphomas such as CLL and FL also had prolonged survival. However, systemic relapses were more frequent in the FL group, occurring in about 80% of patients. Patients with stage IE diffuse large B-cell disease appeared cured of their disease, whereas those with stage IV disease usually died of lymphoma. The worst prognosis was found for PTCL and NKCL, who presented with stage IV disease and died within 3 months. The poor prognosis of PTCL and NKCL has been highlighted in a recent series of cases in the ocular adnexa.[21] Mantle cell lymphoma is an intermediate grade malignancy[20] which occurs uncommonly in the ocular adnexa.[4,5] Both patients with MCL in our study died within

3 years of diagnosis. In contrast to the large recent study by Jenkins *et al.*,[4] our series did not include any patients with lymphoplasmacytoid lymphoma/immunocytoma (LPL). Jenkins *et al.* highlight the difficulty of differentiating LPL from MZL, especially in small biopsies, as both types show an admixture of small lymphocytes and plasma cells.[4] However, a recent Society for Hematopathology Workshop concerning extranodal lymphomas reached consensus that plasmacytoid differentiation is not equivalent to LPL in an extranodal site and recommended that extranodal location is considered a feature of MZL and should argue against a diagnosis of LPL.[19]

The proportion of patients presenting with ocular adnexal lymphomas who have prior or concurrent systemic disease at diagnosis ranges from 8% to 32%.[1,2,4,5,15] In our study, 16/70 patients (23%) had secondary lymphoma. Of those with secondary lymphoma, FL and DLBCL were the most common types. As other authors have demonstrated, prognosis with respect to mortality relates strongly to initial stage.[1,3] Of our stage IE patients (regardless of lymphoma subtype), 75% were alive and disease free without development of systemic disease similar to published figures of 86%[1] and 93%.[3] By comparison, over half of the patients presenting with stage IV disease died of lymphoma.

Development of systemic or extraocular disease has been reported in 33% to 55% of patients in other series of ocular adnexal lymphoproliferative lesions[1,2,4] similar to our figure of 39%. The risk of developing systemic lymphoma in our study was lowest in MZL, intermediate for DLBCL and high for FL and the higher-grade lesions including MCL, PCTL and NKCL.

Most patients (79%) with lymphoma in our series were stage IE. Although the majority of our stage IE patients had a diagnosis of MZL, there were four patients with DLBCL of orbit or lacrimal sac who appeared to have truly localized extranodal disease, and have responded to combination chemotherapy and local radiotherapy with median disease-free survival of 30 months. This phenomenon of localized orbital DLBCL, which responds to therapy, has previously been described by other authors.[5]

Although some authors have stressed the influence of site on prognosis with eyelid and orbital disease having a worse outcome with respect to development of systemic disease or death,[1] compared with conjunctival disease, multivariate analysis failed to show that site was a significant predictor of mortality in our series.

Lymphoproliferative lesions of the ocular adnexa, including both hyperplasia and malignant lymphoma, are not uncommon lesions encountered in ophthalmological practice. As tissue samples from biopsies are often small, and distinction of diffuse hyperplasia from MZL lymphoma may be difficult without demonstration of monoclonality, we recommend to our surgeons that all specimens be submitted fresh to the pathology laboratory. This provides tissue for routine histopathology as well as phenotyping by flow cytometry, which is more sensitive than demonstrating light chain restriction (monoclonality) by immunohistochemistry on paraffin sections. Lymphoma type according to the REAL classification and stage of disease allows accurate prediction of risk of lymphoma-related mortality and development of systemic disease.

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