

Ocular adnexal diffuse large B-cell lymphoma: local disease correlates with better outcomes

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Abstract

Purpose To describe the clinical, immunohistochemical and prognostic features, as well as outcomes of a large series of patients with orbital and periorbital diffuse large B-cell lymphoma (DLBCL). **Design** This study is a multicentre, retrospective non-comparative consecutive case series.

Methods The setting for this study was institutional. A total of 37 consecutive patients identified from the institutions' databases with periorbital and orbital DLBCL were enrolled in the study. A retrospective chart review was used for observation. The main outcome measures were patient demographics, clinical features, imaging, immunohistochemical and histopathological data, treatments administered, and survival.

Results A total of 20 out of 37 cases (54.1%) represented localised periorbital disease (group L), 11 of 37 (29.7%) had systemic disease at presentation with periorbital disease (group S1), and 6 of 37 (16.2%) had previous history of systemic lymphoma (group S2). In all, 28 out of 30 (93.3%) patients were CD20+, 5 of 25 (20%) were CD3+, and 11 of 11 (100%) were CD79a+ (varying denominators reflect the different numbers of patients tested). A total of 25 out of 32 patients (78.1%) received chemotherapy, 14 (43.8%) received rituximab plus chemotherapy, and 19 (59.3%) received radiotherapy. Nine deaths occurred, one in group L (not lymphoma related), six in group S1, and two in group S2. Five-year Kaplan–Meier survival estimates were 55.9% for all cases, 90.9% for group L, 36.0% for group S1, and 0% for group S2. One-year progression-free survival estimates in groups S1 and S2 combined were

58.3% for patients treated with rituximab and 28.6% for those who were not.

Conclusions To our knowledge, this report represents the largest series of patients with periorbital and orbital DLBCL in the literature. The difference in survival between groups L, S1 and S2 was striking, reflecting the grave prognosis of systemic DLBCL, but conversely the relatively optimistic outlook for patients with localised disease. Rituximab plus chemotherapy may be associated with increased survival.

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Introduction

Primary lymphoproliferative disease of the orbit is a heterogeneous condition,^{1–3} representing a spectrum of disease from lymphoid hyperplasia, through indolent lymphomas, such as extranodal marginal zone lymphoma (EMZL) and follicular lymphoma, to more malignant types, such as diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma.⁴ Ocular adnexal lymphoma (OAL) is the most common primary orbital malignancy in adults,⁵ representing 4–13% of all orbital tumours in various orbital series;^{6–11} however, OAL constitutes only ~2% of all lymphomas in general.^{5,12}

The classification of lymphoma has been the subject of much controversy.¹³ More recently, the World Health Organisation classification of lymphoma,¹⁴ based on the previous Revised European American Lymphoma (REAL) classification,¹⁵ has

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provided a useful framework for clinicians and researchers to apply to this broad category of disease;¹³ differentiation of lymphoma types occurs on histological, immunophenotypic, molecular genetic, and clinical grounds. Extranodal disease, such as OAL, has been included in classifications since the establishment of the REAL classification in 1994.^{13,15}

DLBCL represents the most common lymphoma systemically, being responsible for approximately one-third of all lymphoid malignancies¹⁶ and forms part of the spectrum of high-grade lymphoma. Owing to its clinical, histopathological, genetic, and immunohistochemical heterogeneity,^{13,16,17} DLBCL is unlikely to represent a single disease process and has a varied prognosis in studies of the condition.¹⁶ After appropriate staging of disease, treatment for the condition continues to involve chemotherapy, typically an anthracycline-based regimen such as CHOP (cyclophosphamide, adriamycin, vincristine, prednisolone) and/or radiotherapy, although newer immunotherapies such as anti-CD20 antibodies may revolutionise management of the condition and improve the overall prognosis.^{16,18,19}

Orbital and periorbital DLBCL is an uncommon entity, representing 7–21% of primary OAL in several case series,^{3,5,17} but 33% of secondary orbital lymphoma.²⁰ Its clinical, histopathological, immunohistochemical, and prognostic features, as well as outcomes are not well characterised in the literature. Therefore, we conducted a retrospective, multicentre study to report our experience of the condition.

Methods

This was a retrospective, international, four-centre study, involving the Royal Adelaide Hospital (Australia), Manchester Royal Infirmary (UK), LV Prasad Eye Institute (Hyderabad, India), and the M.D. Anderson Cancer Centre (USA). Patients with orbital or periorbital involvement by DLBCL (localised or systemic) between 1997 and 2007 were identified from the respective institutions' databases. Chart review of the identified cases was undertaken. Investigators at each centre entered data pertaining to the following into a standardised spreadsheet: demographic details, medical and ophthalmic history, examination and imaging findings, histopathology, immunohistochemistry, various treatment modalities, follow-up, and mortality.

Statistical analysis

Descriptive statistics were computed for all recorded variables. A subgroup analysis to gauge differences between localised and systemic diseases was undertaken.

We used Spearman's rank correlation coefficient to assess the associations between variables. Kaplan–Meier survival curves were generated. Stata (version 8.0; Stata Corporation, College Station, TX, USA) was used to conduct the analyses.

Results

Patient and disease characteristics

A total of 37 cases with orbital involvement by DLBCL were identified. In all, 20 out of 37 (54.1%) cases represented localised, primary orbital/periorbital DLBCL (group L) (including up to stage 2, Ann Arbor classification), and 17 (45.9%) cases represented systemic disease (group S) with orbital/periorbital involvement. Of these 17 cases, the initial presentation of 11 patients (29.7%) was orbital/periorbital; subsequent staging investigations identified the disease to be part of a systemic lymphomatous process (group S1). The remaining six patients (16.2%) were already known to have systemic lymphoma, their orbital/periorbital presentation representing further dissemination of known disease (group S2), occurring at a median of 50 months (range: 19.6–192 months) after initial diagnosis. The mean age at presentation was 64.1 years (median 69 years, range: 7–89 years) and the male to female ratio was 22:15. A total of 32 patients were Caucasian and 5 were Asian (all from LV Prasad Eye Institute). The mean age at presentation in group L was 61.2 years (range: 7–86 years) and 67.1 years (range: 36–89 years) in group S.

Disease was present unilaterally in 35 of 37 cases, with 2 of 37 cases having bilateral disease at presentation. The most common presentations were the presence of an orbital or eyelid mass (19 patients, 51.4%), proptosis (20 patients, 54.1%), and globe displacement (18, 48.6%) with pain being a feature in 8 patients (21.6%); 50% of patients had more than one symptom; other common features included diplopia, visual symptoms, and epiphora. Visual acuity in the affected eye at presentation was better than or equal to 6/12 in 17 patients, 6/18 to 6/60 in 7 patients, and 3/36 to no perception of light in 7 patients (no data, 6 patients). Information regarding the site of the periorbital disease on radiological imaging was available for 36 of 37 cases. The site of disease involved the orbit in 34 patients and was confined to the lids in 2 patients (both upper lid and eyebrow involvement). Of the 34 orbital cases, 9 were further characterised as intraconal (including 1 bilateral case) of which 3 were apical and a further 2 extended extraconally; 4 cases involved the lacrimal gland. Imaging evidence of bony involvement was observed in 6 patients (3 in group L), with sinus involvement in 10 patients (7 in group L). Of these 10 patients, the ethmoid sinus was involved in 4 cases, the

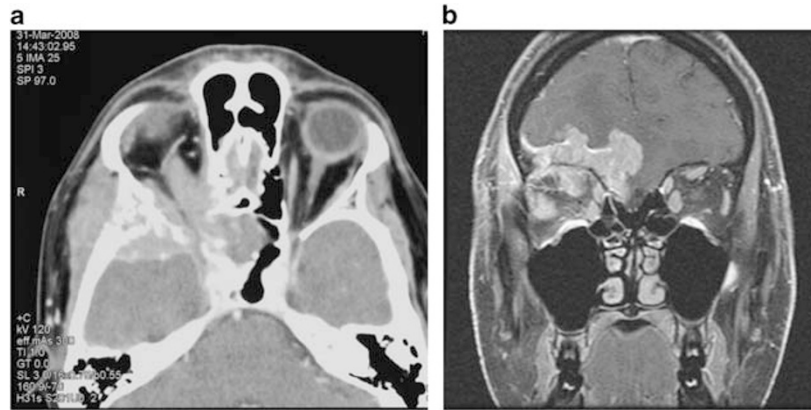


Figure 1 (a) Showing a contrast-enhanced, axial computed tomography scan of a right orbital mass with extensive bony destruction of the right lateral orbital wall and sphenoid sinus, with extension into the middle cranial fossa and temporal fossa. (b) (same patient as in panel a) Showing a coronal, contrast-enhanced fat-suppressed T1-weighted magnetic resonance imaging scan demonstrating extensive invasion of the anterior cranial fossa.

ethmoid and sphenoid sinus in 1, and the maxillary sinus in 3 cases (no data available for 2 cases). Bony erosion was observed in 7 of 37 patients (18.9%) (see Figure 1).

Although there was a low positive correlation (0.41, $P = 0.02$) between the presence of an RAPD and proptosis in all included patients, no other significant correlations were found between the various recorded clinical features. In addition, correlation analysis showed no clinical findings that were more correlated with localised or systemic disease.

Imaging modalities and histopathological examination

Various different imaging modalities were used to evaluate the stage of disease reflecting the many different collaborating units. Computed tomography (CT) was performed in 30 cases (81.8%), magnetic resonance imaging (MRI) in 17 cases (45.9%, including 3 cases not examined by CT), and positron emission tomography (PET) in 13 (35.1%) (including 1 case of secondary, cutaneous lymphoma affecting the periorbital region, not otherwise examined by CT or MRI) (no data, 3 cases). The site of diagnostic biopsy varied between cases, with 25 cases undergoing orbital biopsy (including 3 lacrimal gland biopsies), 2 undergoing nasolacrimal system biopsy, 1 an eyelid biopsy, 1 a conjunctival biopsy, and 3 undergoing sinonasal biopsies. In five cases, biopsies were obtained from other tissues, including the abdomen, skin, and tongue. Bone marrow examination was negative for DLBCL at the time of orbital involvement in 23 cases, positive in 4 cases, and was not performed in 1 case; there were insufficient data regarding bone marrow status in 9 patients.

A histopathological diagnosis of DLBCL was obtained in all cases, although evidence of either transformation

Table 1 Summary of immunohistochemical markers of disease ($n = 37$)

	Positive	Negative	Not performed
<i>Marker</i>			
CD20	28	2 ^a	7
CD79a	11	0	26
CD3	5	20	12
CD10	8	11	18
CD23	1	8	28
CD30	4	7	26
CD43	4	0	33
Bcl-2	10	5	22
Bcl-6	8	5	24

^aOf these two patients negative for the B-cell marker CD20, one patient represented a diffuse large B-cell transformation from mycosis fungoides and had secondary involvement of the upper eyelid and eyebrow. In this case, there was weak positive staining for CD3, but negative staining for CD30, weak positive staining for CD5 and CD4, negative staining for CD8, and positive staining for CD25. The other patient also had secondary involvement of the eyebrow and upper eyelid from a systemic DLBCL; there was positive staining for CD30, but negative staining for CD3, CD4, CD8, CD25, and ALK-1 protein.

from low-grade lymphoma (small-cell lymphoma in one patient, mycosis fungoides in another) or the metachronous presence of follicular lymphoma (three cases) was present in a total of five cases (13.5%) after staging investigations were complete.

Immunohistochemical data for the 37 patients are summarised in Table 1.

Treatment

Table 2 summarises the various different treatment modalities for patients in both groups L and S. Chemotherapy was given in 26 cases and was planned in

Table 2 Summary of the treatment modalities received by patients with DLBCL of the orbit

Treatment	No. of patients
<i>(a) Treatments received by patients with localised disease</i>	
Systemic chemotherapy	1
Systemic chemotherapy and rituximab	4
Systemic chemotherapy and local radiotherapy	4
Systemic chemotherapy, local radiotherapy, and surgical debulking of disease	1
Systemic chemotherapy, rituximab, and local radiotherapy	3
Local radiotherapy, with systemic chemotherapy and rituximab planned	1
Local radiotherapy and surgical debulking	1
Local radiotherapy, with systemic chemotherapy planned	1
Referred to another institution for treatment, no follow-up available	3
Unknown	1
<i>(b) Treatments received by patients with systemic disease</i>	
Systemic chemotherapy	3
Systemic chemotherapy and rituximab	2
Systemic chemotherapy, rituximab, and surgical debulking	1
Systemic chemotherapy and radiotherapy to other disease	1
Systemic chemotherapy, local radiotherapy, and surgical debulking	1
Systemic chemotherapy, rituximab, and local radiotherapy	4
Complete resection of orbital mass	1
Radiotherapy	2
Referred to another institution for treatment, no follow-up available	1
Treatment refused	1

1 further case; a further patient was deemed too frail for chemotherapy, but received radiotherapy. Treatment regimens were varied and included CHOP in 17 cases (with rituximab in 13 cases, 'R-CHOP', see below), VAPEC-B (vincristine, adriamycin, prednisolone, cyclophosphamide, bleomycin) in 3 cases (followed by adriamycin and cyclophosphamide in 2), 2 cycles of hyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine, mesna, and methotrexate) in 1 case, followed by CHOP, CEPP (cyclophosphamide, etoposide procarbazine, and prednisone) in 1 case, CHOP with cytarabine and gemcitabine in 1 case, CHOP followed by ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin) in 1 case, and vincristine/cyclophosphamide in another. Anti-CD20 antibody immunotherapy (rituximab) was given to a total of 14 patients in addition to other treatments (R-CHOP in 13 patients), with 1 further treatment planned. No patients underwent

bone marrow transplantation during the documented follow-up.

Local radiotherapy was documented as having been used in 18 cases (in addition to systemic chemotherapy in 14 cases, with ≥ 2 combination treatments planned), used for metachronous pelvic disease in 1 case and not used in 12 cases, with 2 further cases being referred for treatment elsewhere (no information for 4 cases). Surgical debulking of orbital disease was performed in five cases, in combination with other treatments as detailed in Table 2.

Information regarding an objective initial response to treatment was available in 28 cases. One patient died a day after starting chemotherapy (VAPEC-B). In all, 21 of 28 cases were observed as having a good or excellent response to treatment, 1 had a partial response, and in a further patient the response was deemed poor. In further four cases, initial therapy was proceeding at the time of data collection and it was considered too early to provide any meaningful information.

Mortality and recurrence-free survival rates

The length of follow-up from the diagnosis of orbital/periorbital DLBCL to death or to the last contact ranged from 0 (patients referred elsewhere for treatment) to 132 months, with a mean of 23.0 months (median 10.0 months). The period of progression-free survival, defined as the length of time from the date of histopathological diagnosis of DLBCL to the date of first progression (or most recent follow-up, in the absence of progression), ranged from 0 (patients with no response to treatment) to 132 months. There were 9 deaths (all-cause mortality), 1 of which was in group L and 8 of which were in group S (6 deaths in group S1 and 2 deaths in group S2), with 20 patients remaining alive at the end of the study (8 patients unknown).

Calculations by the Kaplan–Meier method yielded a 5-year progression-free survival estimate of 52.6% for all cases of orbital/periorbital DLBCL combined, but an estimate of 100% for patients with localised DLBCL (no case of progression noted in group L over a mean follow-up of 29.7 months (median 13.0 months)). Five-year survival estimates (all-cause mortality), again by the Kaplan–Meier method, were 55.9% (95% confidence intervals, 24.3–78.8%, see Figure 2) for all patients included in the study, were 90.9% (50.8–98.7%) for patients presenting with DLBCL localised to the orbit (group L), and were 23.5% (1.5–60.6%) for patients with systemic disease (group S) (see Figure 3). Further analysis of group S yielded a Kaplan–Meier estimate for 5-year survival of 36.0% in group S1, compared with 0% for group S2. The 1-year progression-free survival estimate for group S1 was 46.7%. No calculation was

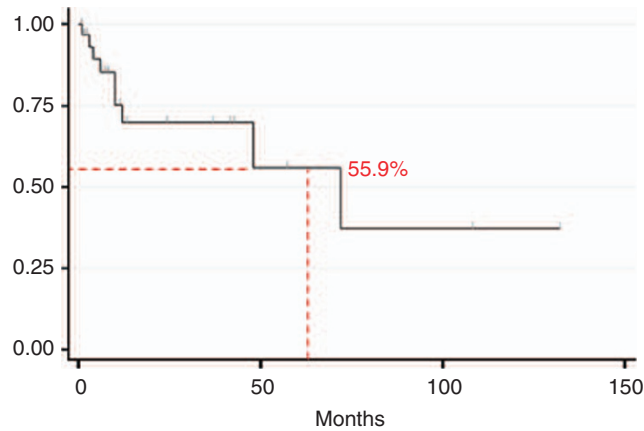


Figure 2 Shows the Kaplan–Meier survival curve for all-cause mortality for all patients included in the study.

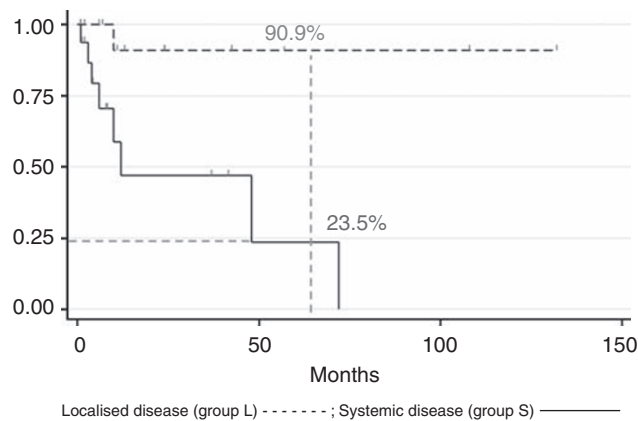


Figure 3 Shows the Kaplan–Meier survival curve for all-cause mortality for patients in group L (localised disease) *vs* group S (systemic disease).

performed for group S2 as this group was already deemed to be progressing (history of systemic lymphoma).

In group S, an initial response to treatment did not correlate with a favourable outcome: four patients were observed to have an initial satisfactory (or good) response to treatment before relapse and death, whereas four others with an initial complete response to treatment were alive at the end of follow-up. In two of the four patients who died, treatment was suboptimal owing to patient frailty or initial refusal of an appropriate treatment modality; in a third patient, CHOP had been used as the therapy for initial disease and was used again, this time in combination with cytarabine, intrathecal methotrexate, and local irradiation. In group L, one patient failed to respond satisfactorily to chemotherapy (R-CHOP plus intrathecal methotrexate), but responded well to subsequent radiotherapy (recurrence-free with 13 months follow-up).

In group S, the mean age of patients treated with rituximab (in combination with other therapies) was 71.6 years, compared with 63.1 years in those treated without rituximab; disease characteristics were similar in those treated with or without rituximab. Two deaths subsequently occurred in patients treated with rituximab compare with five in those who were not (excluding those patients who declined treatment); 1-year progression-free survival estimates were 58.3% for patients treated with rituximab and 28.6% for those who were not.

Both patients with bilateral periorbital disease were in group S. One (group S1) was deemed too frail to receive chemotherapy but was irradiated; after an initial response, recurrence occurred at 3 months. The other patient (S1) received R-CHOP and local radiotherapy and was recurrence-free at the end of 36.7 months follow-up.

The two patients with disease localised to the eyelids/eyebrows were both in group S2, with the periorbital

disease representing recurrent systemic lymphoma. One patient, a 79-year-old man received local radiotherapy only, manifesting a partial response to treatment and was alive at the end of 7.7 months of follow-up, although with progressive disease. The other, a 43-year-old man underwent complete resection of the periorbital lesion, with no adjuvant radiotherapy of chemotherapy; he experienced local and systemic recurrence but remains alive, although with disease, 30 months later.

Discussion

To our knowledge, this report details the largest series of patients with orbital/periorbital DLBCL in the literature. The difference in survival between patients presenting with localised and systemic diseases is striking, reflecting the grave prognosis associated with dissemination of this type of high-grade lymphoma, which was observed in 46% of patients in this cohort. In contrast, a better prognosis was observed for patients with localised disease, treated with combination chemotherapy in some cases solidified by radiotherapy to the orbit. Owing to the rarity of DLBCL in this region, a multicentre study was required to recruit the above-mentioned 37 cases. In addition to providing sufficient cases for analysis, this study design ensured a broad spectrum of patient demographics and treatments, from which we believe important conclusions can be drawn; however, we acknowledge that this was a retrospective study with consequent inherent weaknesses.

Our most significant finding was the exceptionally high survival rate of patients with localised orbital/periorbital DLBCL at presentation (20 patients, 54%), with a 5-year Kaplan–Meier survival (all-cause mortality) estimate of 90.9 and 100% estimated progression-free survival at 5 years. Optimism caused by these figures must be tempered by the relatively short mean follow-up period of 29.7 months (median 13.0, range: 0–132 months), but they nevertheless compare remarkably favourably with others studies of primary OAL.^{3,5,17,21,22} In a large, mainly prospectively collected series of 69 cases of OAL, Sullivan *et al*³ found the disease-specific survival rate to be 81% at 5 years, increasing to 94% for cases of primary OAL.³ However, this series consisted of 24 of 69 (35%) cases of EMZL, with only 5 cases (7%) of orbital DLBCL; 5-year estimated survival for OAL with aggressive histology was 36%; however, it is likely that this latter group contained many cases of OAL that were not localised to the orbit at presentation. McKelvie *et al*²¹ reported their results of 73 patients with OAL and a mean follow-up of 42 months, including 8 patients with DLBCL. The 5-year survival estimate for orbital DLBCL was 50%; the series included three patients with known

stage IV disease and thus compares well with our overall 5-year survival estimate of 55.2%. In a retrospective series of 35 cases of OAL with a median follow-up of 47 months, Ahmed *et al* calculated a 5-year survival of 58% for low-grade lymphomas and 69% for high-grade lymphomas, although only 5 cases of DLBCL were included. In a combined prospective and retrospective series of 192 patients, Jenkins *et al*²³ estimated a 5-year proportion without lymphoma-related death for 19 patients with orbital DLBCL of 50%; however, this study included patients from the early 1990s (or earlier), which limits the relevance of comparison with other more contemporaneous studies; nevertheless, it compares well with figures obtained from both the study by McKelvie *et al* and with our data. In a further retrospective series from the same group, 225 patients with solely ocular adnexal disease were estimated to have a 5-year survival rate (lymphoma-related death) of 81%; survival decreased to 63% if disease was localised to the eyelids as compared with 88% for the conjunctiva and 84% for the deep orbit.²⁴ Unfortunately, no information regarding the individual histological subtypes of OAL was provided.

The high survival rate of localised DLBCL in this study may relate to the large proportion of patients receiving chemotherapy as treatment for their disease (13 of 14 treatments completed, 92.9%), in addition to radiotherapy in the majority of cases (see Table 2) and the use of rituximab in addition to CHOP in 7 of 14 (50%) completed treatments. Although radiotherapy alone has been commonly used as a modality for therapy of OAL, systemic chemotherapy is favoured for orbital/periorbital DLBCL.^{13,20} Rituximab is a chimeric mouse human monoclonal antibody to the pan B-cell surface antigen, CD20, inducing apoptosis and lysis of B cells;¹⁹ although reports of successful treatments of orbital lymphomas with this agent are increasing,^{18,25} a firm evidence base for its use in OAL is still lacking. In group L, no patient experienced progression with or without the use of rituximab; however, in group S, rituximab was used in a total of seven patients in combination with various treatments (see Table 2); CD20 positivity was confirmed in all patients before the use of rituximab. Although this was not a randomised trial and as such conclusions could not be drawn, two deaths occurred in patients treated with both rituximab and chemotherapy compared with five in those treated with only chemotherapy; the estimated 1-year progression-free survivals were disparate at 58.3 and 28.6%, respectively. Further evidence for the use of rituximab in OAL is awaited, although there is increasing evidence for the use of rituximab in combination with chemotherapy in diffuse large cell lymphoma in general.^{26–28}

Of the 31 DLBCL cases that initially presented in the periorbital region, 20 (64.5%) were found to be localised at presentation, with 11 (35.5%) having evidence of systemic DLBCL after staging investigations were complete. Hatef *et al*⁵ recently showed that after appropriate staging investigations, 19 of 43 patients (44.1%) with primary OAL were classified as stage IV, interestingly with only 1 of 9 (11.1%) patients with DLBCL being stage IV (the remainder being either stage I or II). They concluded that extraorbital involvement is present at diagnosis in more than half of patients presenting with OAL, thus prompting extensive systemic staging investigations, particularly the uniform use of PET and bone marrow biopsies in all such patients. Although other authors have suggested that, for EMZL at least, extensive staging is not necessary,^{29,30} most studies suggest that detailed staging procedures are a prerequisite to selecting the correct treatment modality for OAL.^{24,31,32} In the current series, the dramatic difference in survival between patients with and without systemic evidence of DLBCL at presentation is strongly supportive of extensive and accurate initial staging. Although PET scanning in our series was only performed in 13 cases and was not responsible for upstaging any case, it is increasingly documented to be superior to CT in the staging of lymphoma^{33,34} and evaluating response of lymphoma to treatment,³¹ and may also be more cost-effective compared with total body CT.³²

OAL of the eyelids is associated with a worse prognosis than that of the conjunctiva, lacrimal gland, and the deep orbit, in that order.²⁴ In this series, only two patients had periorbital DLBCL limited to eyelid/eyebrow tissue, and both were associated with extraorbital systemic disease found on staging. Four patients had DLBCL involving the lacrimal gland, three of which represented localised disease and one was associated with extraorbital systemic disease; none had evidence of progression during follow-up. Intraconal disease was observed in nine patients, for seven of whom DLBCL was systemic in nature (group S). Of these seven, three were apical (nil apical in group L) and five demonstrated an RAPD with associated poor visual acuity. Of the eight patients with an RAPD at presentation, six were in group S, with only two in group L. Of the patients with intraconal disease in group S, four died with an overall estimated 1-year progression-free survival of 44.4%. Although an intraconal mass is an unusual manifestation of lymphoma in the orbit, our experience and data in this paper suggest that this unusual presentation of orbital lymphoma is more commonly associated with DLBCL compared with other more indolent histological subtypes, such as MALT or low-grade follicular

lymphoma. Given the usually rapid growth rate of DLBCL, it is also more likely to witness visual loss and an RAPD associated with DLBCL compared with the more indolent varieties of OAL, such as MALT or follicular lymphoma. As such, DLBCL is also more likely to cause bony erosion of the orbit, again a feature believed to be unusual for other more indolent histological subtypes of lymphoma.

We acknowledge that the retrospective nature of the data in our study is a weakness and was responsible for inadequate follow-up data in several cases. However, because of the paucity of ocular adnexal cases of DLBCL, a prospective series was neither considered nor practical and the significant number of cases identified through this international collaborative effort nevertheless allows some conclusions to be drawn. From our data, DLBCL localised to the orbital/periorbital region, treated using modern combination chemotherapy and immunotherapy, is associated with a good prognosis. However, long-term continued surveillance for the development of disease elsewhere is recommended as more advanced stages of DLBCL with extraorbital dissemination are associated with a dramatic reduction in survival despite therapy.

Summary

What was known before

- The clinical, histopathological, immunohistochemical, and prognostic features and outcomes of ocular adnexal large cell lymphoma are not well characterised in the literature.

What this study adds

- DLBCL localised to the orbital/periorbital region, treated using modern combination chemotherapy and immunotherapy, is associated with a good prognosis,
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Conflict of interest

The authors declare no conflict of interest.

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References

- 1 Bernadini FP, Bazzan M. Lymphoproliferative disease of the orbit. *Curr Opin Ophthalmol* 2007; **18**: 398–401.
- 2 Demirci H, Shields CL, Karatzas EC, Shields JA. Orbital lymphoproliferative tumors. Analysis of clinical features and systemic involvement in 160 cases. *Ophthalmology* 2008; **115**(9): 1626–1631.
- 3 Sullivan TJ, Whitehead K, Williamson R, Grimes D, Schlect D, Brown I et al. Lymphoproliferative disease of the ocular adnexa: a clinical and pathologic study with statistical analysis of 69 patients. *Ophthalm Plast Reconstr Surg* 2005; **21**(3): 177–188.
- 4 Looi A, Gascoyne RD, Chhanabhai M, Connors JM, Rootman J, White VA. Mantle cell lymphoma in the ocular adnexal region. *Ophthalmology* 2005; **112**: 114–119.
- 5 Hatfeg E, Roberts D, McLaughlin P, Pro B, Esmaili B. Prevalence and nature of systemic involvement and stage at initial examination in patients with orbital and ocular adnexal lymphoma. *Arch Ophthalmol* 2007; **125**(12): 1663–1667.
- 6 Demirci H, Shields CL, Shields JA, Honavar SG, Mercado GJ, Tovilla JC. Orbital tumors in the older adult population. *Ophthalmology* 2002; **109**: 243–248.
- 7 Henderson JW, Campbell RJ, Farrow GM, Garrity JA. *Orbital Tumors*, 3rd ed. Raven Press: New York, 1994.
- 8 Rootman J. *Diseases of the Orbit: A Multidisciplinary Approach*. JB Lipincott: Philadelphia, 1988.
- 9 Wilson MW, Buggage RR, Grossniklaus HE. Orbital lesions in the southeastern United States. *Orbit* 1996; **15**: 17–24.
- 10 Kennedy RE. An evaluation of 820 orbital cases. *Trans Am Ophthalmol Soc* 1984; **82**: 134–157.
- 11 Seregard S, Sahlin S. Panorama of orbital space-occupying lesions. The 24-year experience of a referral centre. *Acta Ophthalmol Scand* 1999; **77**: 91–98.
- 12 Lazzarino M, Morra E, Rosso R. Clinicopathologic and immunologic characteristics of non-Hodgkin's lymphoma presenting in the orbit. *Cancer* 1985; **55**: 1907–1912.
- 13 Bardenstein DS. Ocular adnexal lymphoma: classification, clinical disease and molecular biology. *Ophthalmol Clin N Am* 2005; **18**: 187–197.
- 14 Jaffe ES, Harris NL, Stein H. *Pathology and Genetics: Tumours of Haematopoietic and Lymphoid Tissues (WHO Classification of Tumours)*. IARC Press: Lyon, 2001.
- 15 Harris NL, Jaffe ES, Stein H. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994; **84**: 1361–1392.
- 16 Hunt KE, Reichard KK. Diffuse large B-cell lymphoma. *Arch Pathol Lab Med* 2007; **132**: 118–124.
- 17 Ahmed S, Shahid RK, Sison CP, Fuchs A, Mehrotra B. Orbital lymphomas: a clinicopathologic study of a rare disease. *Am J Med Sci* 2006; **331**(2): 79–83.
- 18 Sullivan TJ, Grimes D, Bunce I. Monoclonal antibody treatment of orbital lymphoma. *Ophthalm Plast Reconstr Surg* 2004; **20**(2): 103–106.
- 19 Cvetkovic RS, Perry CM. Rituximab. A review of its use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. *Drugs* 2006; **66**(6): 791–820.
- 20 Esmaili B, Ahmadi MA, Manning J, McLaughlin PW, Ginsberg L. Clinical presentation and treatment of secondary orbital lymphoma. *Ophthalm Plast Reconstr Surg* 2002; **18**(4): 247–253.
- 21 McKelvie PA, McNab A, Francis IC, Fox R, O'Day J. Ocular adnexal lymphoproliferative disease: a series of 73 cases. *Clin Exp Ophthalmol* 2001; **29**: 387–393.
- 22 Nola M, Lukenda A, Bollman M, Kalauz M, Petrovecki M, Bollmann R. Outcome and prognostic factors in ocular adnexal lymphoma. *Croat Med J* 2004; **45**(3): 328–332.
- 23 Jenkins C, Rose GE, Bunce C, Wright JE, Cree IA, Plowman N et al. Histological features of ocular adnexal lymphoma (REAL classification) and their association with patient morbidity and survival. *Br J Ophthalmol* 2000; **84**(8): 907–913.
- 24 Jenkins C, Rose GE, Bunce C, Cree I, Norton A, Plowman PN et al. Clinical features associated with survival of patients with lymphoma of the ocular adnexa. *Eye* 2003; **17**(7): 809–820.
- 25 Kang SJ, Schmack I, Wojno TH, Grossniklaus HE. Composite lymphoma of the orbit treated with rituximab. *Ophthalm Plast Reconstr Surg* 2002; **20**(2): 103–106.
- 26 Miller T, Unger J, Spier C. Effect of adding rituximab to three cycles of CHOP plus involved-field radiotherapy for limited-stage aggressive diffuse large B-cell lymphoma (SWOG-0014). *Blood* 2004; **104**: a158.
- 27 Pfreundschuh M, Trumper L, Osterbord A. CHOP-like chemotherapy plus rituximab vs CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large B-cell lymphoma. *Lancet Oncol* 2006; **7**: 379–391.
- 28 Coiffier B, Lepage E, Briere J. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. *N Engl J Med* 2002; **346**: 235–242.
- 29 Tanimoto K, Kaneko A, Suzuki S, Sekiguchi N, Maruyama D, Kim SW et al. Long-term follow-up results of no initial therapy for ocular adnexal MALT lymphoma. *Ann Oncol* 2006; **17**(1): 135–140.
- 30 Tsang RW, Gospodarowicz MK, Pintilie M, Wells W, Hodgson DC, Sun A et al. Localised mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. *J Clin Oncol* 2003; **21**(22): 4157–4164.
- 31 Martinet S, Ozsahin M, Belkac'emi Y, Landmann C, Poortmans P, Oehlere C et al. outcome and prognostic factors in orbital lymphoma: a rare cancer network study on 90 consecutive patients treated with radiotherapy. *Int J Radiat Oncol Biol Physics* 2003; **55**(4): 892–898.
- 32 Raderer M, Vorbeck F, Formanek M, Oesterreicher C, Valencak J, Penz M et al. Importance of extensive staging in patients with mucosa-associated lymphoid tissue (MALT)-type lymphoma. *Br J Cancer* 2000; **83**(4): 454–457.
- 33 Tatsumi M, Cohade C, Nakamoto Y, Fishman EK, Wahl RL. Direct comparison of FDG PET and CT findings in patients with lymphoma: initial experience. *Radiology* 2005; **237**(3): 1038–1045.
- 34 Schaefer NG, Strobel K, Taverna C, Hany TF. Bone involvement in patients with lymphoma: the role of FDG-PET/CT. *Eur J Nucl Med Mol Imaging* 2007; **34**(1): 60–67.