

Research

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Clinicopathological Features of Ocular Adnexal Mantle-Cell Lymphoma in an International Multicenter Cohort

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 [Invited Commentary](#)

IMPORTANCE To our knowledge, the clinical features of ocular adnexal mantle-cell lymphoma (OA-MCL) have not previously been evaluated in a large multicenter cohort.

OBJECTIVE To characterize the clinical features of OA-MCL.

DESIGN, SETTING, AND PARTICIPANTS This retrospective multicenter study included patient data collected from January 1, 1980, through December 31, 2015, at 6 eye cancer centers in 4 countries. Medical records of 55 patients with OA-MCL were reviewed; the median length of follow-up was 33 months.

MAIN OUTCOMES AND MEASURES Overall survival, disease-specific survival, and progression-free survival were the primary end points.

RESULTS Fifty-five patients were included; ocular adnexal MCL was found to be most common in older individuals (mean age, 70 years) and men (n = 42 of 55; 76%). Patients with OA-MCL frequently presented with disseminated lymphoma (n = 34 of 55; 62%), and were likely to experience stage IVE disease (n = 35 of 55; 64%), with bilateral involvement (n = 27 of 55; 47%), tumor masses (n = 27 of 36; 75%), and involvement of the orbit (n = 32 of 55; 58%). Chemotherapy with or without external beam radiation therapy was the most frequently used treatment. Overall survival rates for the entire cohort were 65% at 3 years (95% CI, 52%-78%) and 34% at 5 years (95% CI, 21%-47%). Disease-specific survival after 5 years was 38% for the entire cohort (95% CI, 25%-51%); the disease-specific survival adjusted by eye cancer center was better in patients who had received rituximab in addition to the chemotherapy regimen (hazard ratio, 3.3; 95% CI, 1.0-14.7; $P = .06$). The median progression-free survival was 2.3 years (95% CI, 1.8-2.7 years) in patients who experienced recurrence after primary treatment, and 4.1 years (95% CI, 3.9-4.3 years) in patients who presented with a relapse of systemic lymphoma in the ocular adnexal region.

CONCLUSIONS AND RELEVANCE These results suggest that the distinctive features of OA-MCL are its appearance in older male individuals, advanced stage and bilateral manifestation at the time of diagnosis, and aggressive course. The prognosis of patients with OA-MCL might be improved by addition of rituximab to chemotherapy treatment.

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Mantle-cell lymphoma (MCL) is a rare type of non-Hodgkin lymphoma that originates in peripheral B cells of the inner mantle zone. It is characterized by chromosomal translocation t(11;14)(q13;q32), which results in upregulation of *BCL-1*, the gene that encodes protein cyclin D-1.¹⁻⁴ Mantle-cell lymphoma accounts for approximately 9% of all cases of non-Hodgkin lymphoma. The annual incidence of this subtype has increased during recent decades to 1 to 2 per 100 000 persons.²

Mantle-cell lymphoma is a disease of older individuals (median age, 71 years) and is more common in men than in women by a ratio of 3:1.^{1,5-8} The clinical course of MCL is typically aggressive; it usually presents with widespread disease and is characterized by frequent recurrences and a poor survival rate.^{1,2,8-10} In the past, management had been limited to palliative therapy, which mainly consisted of anthracycline-based chemotherapy.^{11,12} During recent decades, however, novel strategies combining chemotherapy such as cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (CHOP) with anti-CD20 agent rituximab (R-CHOP) have shown improved response rates and survival rates.^{13,14}

Mantle-cell lymphoma in the ocular adnexa represents 2% to 7% of all non-Hodgkin lymphomas.¹⁵⁻¹⁹ Clinicopathological reports of ocular adnexal MCL (OA-MCL) have been published in only a few studies^{9,20,21} with a limited number of cases (mean, 7), typically involving a single eye cancer center. Therefore, the aim of the present study is to evaluate the clinicopathological features of OA-MCL in a large cohort of patients from 6 eye cancer centers.

Methods

Study Design

Eligible patients with a diagnosis of OA-MCL were identified from the databases of 6 eye cancer centers. The cases were collected via a review of medical records from January 1, 1980, through December 31, 2015.

For histopathological examination, the specimens were stained with hematoxylin-eosin and analyzed immunohistochemically using the following panel of antibodies known to be clinically significant in lymphoma: Bcl-2, Bcl-6, CD3, CD5, CD10, CD20, CD23, and CD79a; cyclin D-1; and MIB-1, an antibody used to establish the presence of Ki-67, a protein associated with cellular proliferation. Because the data collection spanned 36 years and encompassed 6 international eye cancer centers, not all the samples were analyzed in this uniform manner. However, all cancer centers had subsequently reviewed the specimens independently of the study and had reclassified them according to the World Health Organization publication *Classification of Tumours of Haematopoietic and Lymphoid Tissues*²² and, where required, performed additional immunostaining.

The study followed the tenets of the Declaration of Helsinki and the US Health Insurance Portability and Accountability Act of 1996. Institutional review board and health information privacy agency approvals were obtained from the Danish Data Protection Agency and local ethics committees,

Key Points

Question What are the clinical features of ocular adnexal mantle-cell lymphoma (OA-MCL)?

Findings This retrospective multicenter study included 55 patients, largely elderly and male, with stage IVE OA-MCL involving bilateral tumor masses (frequently affecting the orbit). Five-year disease-specific survival was 38%, which can potentially be improved through the addition of rituximab to the chemotherapy treatment.

Meaning Ocular adnexal MCL tends to manifest as bilateral tumor masses of the orbit, most often in men; it has an aggressive clinical course with poor prognosis.

and the study followed standard consent procedures for oral and/or written consent in each location.

Clinical Data

The following clinical data were recorded: age and sex of the patient, symptoms, clinical findings, laterality, systemic involvement according to the Ann Arbor staging classification,²³ year of diagnosis (before or after the US Food and Drug Administration approval of rituximab in 1997), treatment approaches, response to therapy, survival duration, and cause of death.

Systemic involvement and laterality were determined using clinical information and diagnostic tools available at the time of diagnosis. Currently, a complete diagnostic procedure includes a positron emission tomography/computed tomography scan of the entire body, computed tomography or magnetic resonance imaging of the ocular adnexal region, and a bone-marrow biopsy.

Primary ocular adnexal lymphoma is defined as a biopsy-verified lymphoma in the orbit, conjunctiva, lacrimal gland, lacrimal sac, and/or eyelids, without history of systemic lymphoma. Stage IE disease is limited to the ocular adnexal region (where E indicates the involvement of the extranodal site), while stage IIE indicates involvement of unilateral preauricular or submandibular lymph nodes or adjacent structures. Stage IVE indicates involvement of 1 or more organs or tissues outside the lymphatic system. Each sample in the present study was assessed for stage, and the extent of ocular adnexal involvement of primary lymphomas was evaluated according to the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system for ocular adnexa lymphoma.²⁴

Statistical Analysis

Overall survival, disease-specific survival (DSS), and progression-free survival were considered the primary end points. Overall survival was defined as the length of time from the date of diagnosis to the date of death from any cause (or to the date of last contact, a censored event). Disease-specific survival was defined as the time from the date of diagnosis to the date of death from lymphoma (or to the date of last contact, a censored event). Progression-free survival was calculated as the time from the date of diagnosis to either the date of first relapse or first sign of progression after initial treatment; in this

Table 1. Clinical and Staging Characteristics of 55 Patients With Ocular Adnexal Mantle-Cell Lymphoma

Characteristic	Lymphoma Presentation, No. of Patients ^a			
	Total Patients, No. (%)	Primary (n = 8)	Disseminated (n = 34)	Relapsed (n = 13)
Sex				
Male	42 (76)	7	25	10
Female	13 (24)	1	9	3
Age, y				
≤60	5 (9)	0	3	2
>60	50 (91)	8	31	11
Laterality				
Unilateral	29 (53)	6	15	8
Bilateral	26 (47)	2	19	5
Ann Arbor stage				
IE	9 (16)	7	0	2
IIE	5 (9)	1	4	0
IIIE	6 (11)	0	4	2
IVE	35 (64)	0	26	9
Initial treatment				
EBRT	6 (12)	2	3	1
Rituximab				
With CHOP	3 (6)	0	3	0
With CHOP and EBRT	1 (2)	1	0	0
With other chemotherapy	13 (25)	0	9	4
With other chemotherapy and EBRT	2 (4)	0	1	1
With EBRT	1 (2)	0	1	0
Chemotherapy				
CHOP	2 (4)	0	2	0
CHOP and EBRT	2 (4)	0	0	2
Other chemotherapy	11 (22)	0	8	3
Other chemotherapy and EBRT	10 (20)	4	4	2
Recurrence or progression				
No	11 (22)	1	5	5
Yes	40 (78)	7	25	8
Disease status at last follow-up				
Complete remission	13 (24)	1	10	2
Alive with disease	11 (20)	3	6	1
Dead from lymphoma	27 (49)	4	17	6
Dead from other cause	4 (7)	0	1	3

Abbreviations: CHOP, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone; EBRT, external beam radiation therapy.

^a Data are not specified for all patients.

case, the date of death from any cause and the date of last contact were both considered censored events. Kaplan-Meier plots were generated to visualize survival outcomes, and different risk groups were compared using the log-rank test. Individual risk factors were compared using the χ^2 test. Cox proportional hazard modeling was used to estimate each hazard ratio (HR). Statistical calculations were performed using SPSS Statistics version 22 (IBM Corporation).

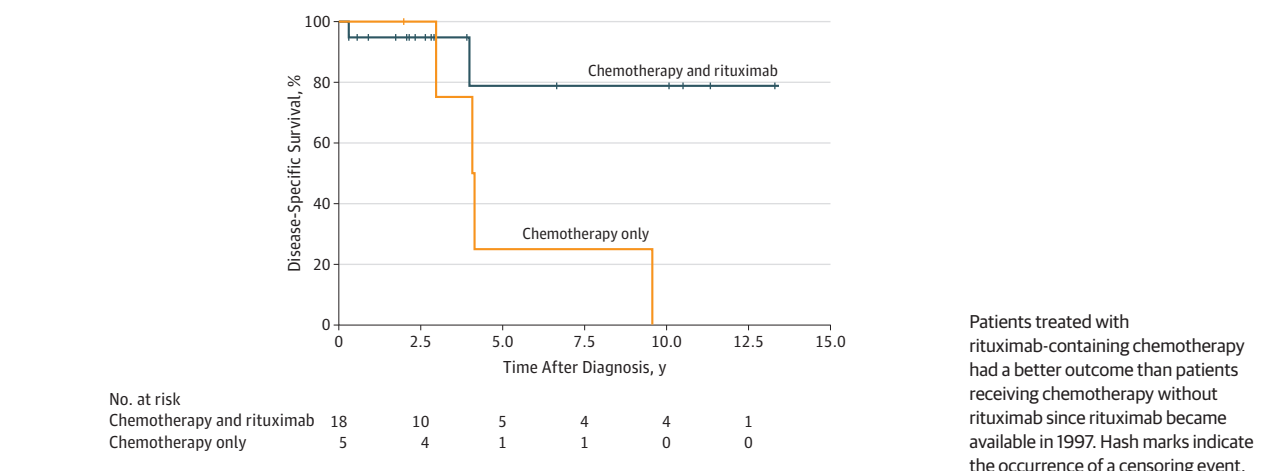
Results

A total of 55 patients with OA-MCL were identified from the databases of eye cancer centers in Copenhagen, Denmark (n = 27); Houston, Texas (n = 14); Liverpool, England (n = 10);

New York, New York (n = 2); Atlanta, Georgia (n = 1); and Melbourne, Victoria, Australia (n = 1). Selected patient data from the cancer centers in Copenhagen, New York, and Houston were previously published in local studies on various histologic subtypes of ocular adnexal lymphoma.^{9,19,25}

Forty-two of the patients were male (76%) (Table 1). The mean age was 70 years (range, 34-90 years), and the median follow-up time was 33 months (range, 1-162 months). The patients were predominantly white (n = 37 of 41; 90%). Tumor or swelling (n = 22 of 29; 76%) and irritation (n = 15 of 29; 52%) were the most common symptoms (Figure 1). The median symptom duration was 6 months (range, 1-24 months). The most common clinical signs were a mass (n = 27 of 36; 75%) and globe displacement (n = 9 of 36; 25%). Serum lactate dehydrogenase levels were available in 19 patients, of whom 12 (63%) had elevated levels.

Figure 1. Disease-Specific Survival Among Patients With Stage IVE Ocular Adnexal Mantle-Cell Lymphoma Treated With Chemotherapy With or Without Rituximab Since 1997



Eight patients (15%) were diagnosed with primary OA-MCL, 34 (62%) had systemic lymphoma with an additional manifestation in the ocular adnexa, and 13 (24%) presented with a relapse of systemic lymphoma in the ocular adnexal region. Of the 8 patients with primary lymphomas, 6 had unilateral disease (75%). Bilateral manifestation was common among patients with disseminated OA-MCL (n = 19 of 34; 56%) and relapsed disease (n = 5 of 13; 38%).

The orbit was the most frequently involved ocular adnexal site among patients with primary OA-MCL (n = 6 of 8; 75%), as well as disseminated (n = 19 of 34; 56%), and relapsed disease (n = 7 of 13; 54%) (Table 2). The conjunctiva was likewise frequently involved in 25% (n = 2 of 8), 35% (n = 12 of 34), and 23% (n = 3 of 13) of primary, disseminated, and relapsed OA-MCL, respectively.

Clinical Staging of OA-MCL

According to the Ann Arbor staging system,²³ 7 of the 8 patients with primary OA-MCL were initially seen with stage IE disease, while patients with disseminated and relapsed OA-MCL predominantly had stage IVE disease at diagnosis (n = 26 of 34, 76%; n = 9 of 13, 69%) (Table 1).

The AJCC TNM staging was performed in the 8 patients with primary lymphomatous disease. Of these patients, 6 had stage T2 disease (involving the orbit with or without the lacrimal gland) and 2 had stage T3 disease (which involved the pre-septal eyelids). The posterior orbit (T2c) was the most frequently involved site in T2 disease, followed by the anterior orbit without the lacrimal gland (T2a). Lymph node involvement (TxNIMx, per AJCC stages) was present in 1 of the 8 patients.

Treatment

Chemotherapy with or without external beam radiation therapy (EBRT) was the most frequently used treatment approach among primary, disseminated, and relapsed lymphomas (50%, 41%, and 53%, respectively) (Table 1). The median prescribed EBRT dose was 30 Gy (range, 4-50 Gy). (To convert to rad, multiply by 100.) The applied chemotherapy types included CHOP, alkylating agents, and chemotherapy unspeci-

fied in medical records. Rituximab in combination with chemotherapy (with or without EBRT) was used in the treatment of 19 of 51 patients in the study (37%), all of whom had stage IVE disease, with the exception of 1 person with disease at stage IE. Among stage IVE lymphomas, this treatment approach was applied more frequently in Houston (n = 10 of 13; 77%) compared with the remaining eye cancer centers (n = 8 of 20; 40%) (Table 3).

Treatment Outcomes and Survival

Median follow-up time was 33 months (range, 1-162 months). Recurrence or progression was observed in 84% of patients (32 of 38; 95% CI, 72-96) after primary treatment, and in 62% of patients (8 of 13; 95% CI, 36-88) who presented with a relapse of systemic lymphoma in the ocular adnexal region (Table 1). The median progression-free survival was 2.3 years (95% CI, 1.8-2.7 years) and 4.1 years (95% CI, 3.9-4.3 years), respectively. The site of relapse was accessible in 29 patients with OA-MCL, of whom 8 had recurrence within the ocular adnexal region (5 of these had involvement in the orbit), 14 had ocular adnexal recurrence in conjunction with nodal and/or extranodal involvement, and 7 had recurrence in nodal and/or extranodal sites outside the ocular adnexal region.

Survival data were available for all 55 patients. The OS rates for the entire cohort were 65% at 3 years (95% CI, 52%-78%) and 34% at 5 years (95% CI, 21%-47%). The 3-year and 5-year DSS rates were 72% (95% CI, 60%-84%) and 38% (95% CI, 25%-51%), respectively.

The 5-year DSS was not significantly different in patients with primary, disseminated, or relapsed lymphoma and was likewise not associated with Ann Arbor stage of disease (P = .27 and P = .42, respectively). The 5-year DSS was better among patients with disseminated lymphoma diagnosed after 1997 (57%; 95% CI, 42%-72%) than those diagnosed before 1997 (22%; 95% CI, 9%-35%) (P = .04). Since rituximab treatment became available in 1997, patients with stage IVE disease receiving rituximab in addition to chemotherapy (with or without EBRT) had a better 5-year DSS (79%; 95% CI, 65%-93%) than patients who were not treated with rituximab (25%; 95% CI, 11%-39%)

Table 2. Location, Frequency of Symptoms, and Clinical Signs at Presentation of Ocular Adnexal Mantle-Cell Lymphoma

Characteristic	Lymphoma Presentation, No. of Patients ^a			
	Total Patients, No. (%)	Primary (n = 8)	Disseminated (n = 34)	Relapsed (n = 13)
Location in the ocular adnexal region				
Orbit	32 (58)	6	19	7
Conjunctiva	17 (31)	2	12	3
Lacrimal gland	8 (15)	0	7	1
Eyelid	9 (16)	2	6	1
Lacrimal sac	1 (2)	0	0	1
Symptom				
Tumor or swelling	22 (76)	2	10	10
Irritation or pain	15 (52)	2	8	5
Epiphora	13 (45)	2	6	5
Exophthalmus	5 (17)	1	3	1
Diplopia	6 (21)	0	6	0
Ptosis	3 (10)	0	2	1
Decreased visual activity	1 (3)	0	1	0
B symptoms ^b	6 (21)	0	5	1
Not stated	26 (47)	6	17	3
Clinical sign				
Mass	27 (75)	2	16	9
Globe displacement	9 (25)	2	6	1
Chemosis	7 (19)	2	4	1
Restricted eye movement	4 (11)	1	3	0
Resistance	2 (6)	1	1	0
Edema	2 (6)	0	1	1
Diplopia	6 (17)	1	5	0
Ptosis	2 (6)	0	1	1
Epiphora	3 (8)	1	2	0
Not stated	19 (35)	6	10	3

^a A total of more than 100% because patients may have presenting symptoms or signs in more than one location.

^b B symptoms are defined as night sweats, fever, and weight loss.

Table 3. Treatment and Outcome of Patients With Mantle-Cell Lymphoma in All Eye Cancer Centers

Status	Eye Cancer Center, Patients, No. (%) ^a							
	Copenhagen, Denmark		Houston, Texas		Liverpool, England		Other ^b	
	<IVE	IVE	<IVE	IVE	<IVE	IVE	<IVE	IVE
Total	9	18	1	13	8	2	2	2
Treatment								
EBRT	2 (25)	0	1 (100)	0	0	2 (100)	0	1 (50)
CTX ± EBRT	5 (63)	9 (53)	0	2 (15)	8 (100)	0	1 (50)	0
Rituximab and CTX ± EBRT	1 (11)	8 (47)	0	10 (77)	0	0	0	0
Rituximab and EBRT	0	0	0	1 (8)	0	0	0	0
Status at last follow-up								
Complete remission	3 (33)	5 (28)	0	2 (15)	0	0	1 (50)	2 (100)
Alive with disease	2 (22)	1 (6)	0	6 (46)	1 (13)	0	1 (50)	0
Died of lymphoma	4 (44)	11 (61)	1 (100)	2 (15)	7 (88)	2 (100)	0	0
Died of other causes	0	1 (6)	0	3 (21)	0	0	0	0

Abbreviations: CTX, chemotherapy; EBRT, external beam radiation therapy.

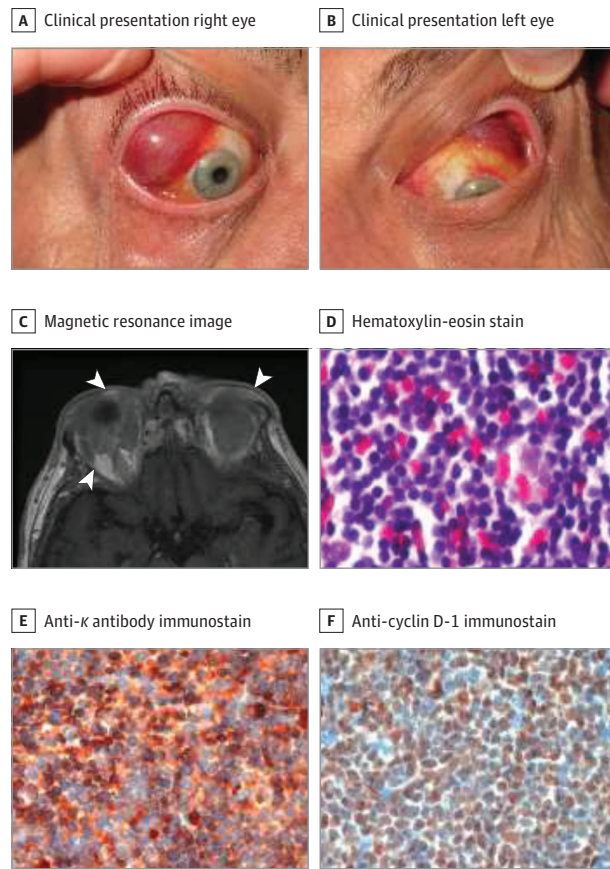
^a Data are not specified for all patients.

^b Other locations are Atlanta, Georgia; New York, New York; and Melbourne, Victoria, Australia.

($P = .04$) (Figure 2). The 5-year DSS was better among patients with disseminated lymphoma from Houston (100%) than from Liverpool (0%; $P = .01$) and was more favorable for patients with

stage IVE disease from Houston (100%) than patients with stage IVE disease from Copenhagen (28%; $P = .005$) (Table 3). After adjusting for eye cancer center, patients receiving rituximab in

Figure 2. Clinical, Magnetic Resonance Imaging, and Histological Findings of Mantle-Cell Lymphoma



A and B, Clinical presentation of mantle-cell lymphoma with bilateral involvement of the conjunctiva. C, Image shows conjunctival and orbital tumor masses (arrowheads). D, Mantle-cell lymphoma showing a monotonous pattern of small cells with irregular nuclei with inconspicuous nucleoli and scant cytoplasm. E, The tumor cells bind anti- κ antibodies. F, The tumor cells react with anti-cyclin D-1.

addition to chemotherapy (with or without EBRT) had a better disease-specific survival at 5 years than patients who did not receive rituximab (HR, 3.3; 95% CI, 1.0-14.7; $P = .06$).

Discussion

Ocular adnexal MCL was found to present primarily in older male individuals, and it appeared to be an aggressive malignant condition with a frequent occurrence of dissemination (62%; 95% CI, 49%-75%), bilateral ocular adnexal manifestation (47%; 95% CI, 34%-60%), and a poor prognosis (5-year DSS, 38%; 95% CI, 24%-50%), which could potentially be improved by addition of rituximab to the chemotherapy regimen.

The predominance of OA-MCL among older male individuals, as detected in this study, is consistent with the results of previous research.^{1,5-8} The sex difference associated with this disease is among the most pronounced in lymphoma, with a similar male predominance found only in hairy-cell leukemia (which has a male-female ratio of 3.3:1) and Burkitt lymphoma (with a

male-female ratio of 3.1:1).²⁶ Genetic studies propose that this striking sex difference might be explained by an age-related effect in older cells that increases the risk of loss of sections of the Y chromosome, in combination with the suppression of a tumor suppressor gene on the X chromosome.²⁷

The high proportion of disseminated lymphoma identified in the present study is likewise in accordance with previous studies of MCL.^{1,2,8,9} The tendency for lymphoma to disseminate throughout the body is probably related to the derivation of MCL from pregerminal center B lymphocytes, which express specific adhesion molecules and chemokine receptors that allow them to circulate continuously to secondary lymphoid tissues.²⁸ This predisposition toward widespread disease likely explains the high proportion of bilateral disease identified among OA-MCLs in this study.

Current lymphoma treatment guidelines recommend R-CHOP or similar chemotherapy for management of MCL at all stages.² This approach was only used to treat 19 patients in the present study, which might be because the study spanned a 36-year period, and rituximab has only been available since 1997.²⁹

The presented data confirm that MCL has a poor prognosis.^{1,15,16,30-32} As other studies have shown, survival can potentially be improved by the addition of rituximab to chemotherapy treatment.^{13,14} The fact that patients from Houston had a better outcome than patients from Liverpool and Copenhagen may be explained in part by the higher proportion of patients from Houston who were diagnosed after 1997 and who consequently received rituximab in combination with chemotherapy. Studying patients with primary OA-MCL across relatively similar lengths of the follow-up period established that all had recurrences after treatment except 1 patient, who had received rituximab-containing chemotherapy. Therefore, the present findings highlight the importance of adding rituximab to the chemotherapy treatment, including in patients whose OA-MCL is localized.

Limitations

The retrospective design of this multicenter study poses some inherent limitations. The data were pooled across 6 oncology centers over a 36-year period, which entailed incomplete medical records and varying diagnostic and treatment methods, which made evaluation of treatment approaches particularly challenging. As the present study deals with a rare subtype of lymphoma in the ocular adnexa, the number of patients is low. This makes it less certain that these findings are truly representative. Furthermore, the median follow-up was 33 months, which might not have been enough time to detect the outcome variables in some cases. On the other hand, multicenter studies like this, obtaining a reasonable number of patients, provide valuable information on relatively rare lesions such as OA-MCL.

Conclusions

The results of this study confirm that OA-MCL manifests most commonly in older men. The clinical course of this disease

appears to be aggressive, with patients frequently presenting with disseminated lymphoma at stage IVE, with bilateral tumor masses that frequently involve the orbit. Treatment commonly requires chemotherapy, with or without EBRT. These data suggest that the prognosis for these patients is poor; how-

ever, the findings suggest that survival can potentially be improved by addition of rituximab to the chemotherapy regimen. Further research is necessary to identify more clinical features associated with earlier detection of MCL in patients with OA-MCL to potentially improve their prognosis.

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Author Contributions: Dr Knudsen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: Knudsen, Heegaard, Coupland, Esmaeli, Finger, Graue, Grossniklaus, Khong, McKelvie, Mulay, Sjø, Vemuganti, Thuro, Curtin.

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Study supervision: Heegaard, Rasmussen, Coupland, Esmaeli, Finger, Graue, Ralfkiaer.

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REFERENCES

- Rasmussen PK. Diffuse large B-cell lymphoma and mantle cell lymphoma of the ocular adnexal region, and lymphoma of the lacrimal gland: an investigation of clinical and histopathological features. *Acta Ophthalmologica*. 2013;91 (thesis 5):1-27.
- Dreyling M, Geisler C, Hermine O, et al; ESMO Guidelines Working Group. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014;25(suppl 3):iii83-iii92.
- Oka K, Ohno T, Yamaguchi M, et al. PRAD1/Cyclin D1 gene overexpression in mantle cell lymphoma. *Leuk Lymphoma*. 1996;21(1-2):37-42.
- Vaandrager JW, Schuurings E, Zwijkstra E, et al. Direct visualization of dispersed 11q13 chromosomal translocations in mantle cell lymphoma by multicolor DNA fiber fluorescence in situ hybridization. *Blood*. 1996;88(4):1177-1182.
- Andersen NS, Jensen MK, de Nully Brown P, Geisler CH. A Danish population-based analysis of 105 mantle cell lymphoma patients: incidences, clinical features, response, survival and prognostic factors. *Eur J Cancer*. 2002;38(3):401-408.
- Chandran R, Gardiner SK, Simon M, Spurgeon SE. Survival trends in mantle cell lymphoma in the United States over 16 years 1992-2007. *Leuk Lymphoma*. 2012;53(8):1488-1493.
- Samaha H, Dumontet C, Ketterer N, et al. Mantle cell lymphoma: a retrospective study of 121 cases. *Leukemia*. 1998;12(8):1281-1287.
- Tiemann M, Schrader C, Klapper W, et al; European MCL Network. Histopathology, cell proliferation indices and clinical outcome in 304 patients with mantle cell lymphoma (MCL): a clinicopathological study from the European MCL Network. *Br J Haematol*. 2005;131(1):29-38.
- Rasmussen P, Sjø LD, Prause JU, Ralfkiaer E, Heegaard S. Mantle cell lymphoma in the orbital and adnexal region. *Br J Ophthalmol*. 2009;93(8):1047-1051.
- Fernández V, Salamero O, Espinet B, et al. Genomic and gene expression profiling defines indolent forms of mantle cell lymphoma. *Cancer Res*. 2010;70(4):1408-1418.
- Barista I, Romaguera JE, Cabanillas F. Mantle-cell lymphoma. *Lancet Oncol*. 2001;2(3):141-148.
- Witzig TE. Current treatment approaches for mantle-cell lymphoma. *J Clin Oncol*. 2005;23(26):6409-6414.
- Schulz H, Bohlius J, Skoetz N, et al. Chemotherapy plus rituximab versus chemotherapy alone for b-cell non-Hodgkin's lymphoma. *Cochrane Database Syst Rev*. 2007;(4):CD003805.
- Geisler CH, Kolstad A, Laurell A, et al; Nordic Lymphoma Group. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. *Blood*. 2008;112(7):2687-2693.
- Kirkegaard MM, Coupland SE, Prause JU, Heegaard S. Malignant lymphoma of the conjunctiva. *Surv Ophthalmol*. 2015;60(5):444-458.
- Kirkegaard MM, Rasmussen PK, Coupland SE, et al. Conjunctival lymphoma—an international multicenter retrospective study. *JAMA Ophthalmol*. 2016;134(4):406-414.
- Ferry JA, Fung CY, Zukerberg L, et al. Lymphoma of the ocular adnexa: a study of 353 cases. *Am J Surg Pathol*. 2007;31(2):170-184.
- Sjø LD, Ralfkiaer E, Prause JU, et al. Increasing incidence of ophthalmic lymphoma in Denmark from 1980 to 2005. *Invest Ophthalmol Vis Sci*. 2008;49(8):3283-3288.
- Graue GF, Finger PT, Maher E, et al. Ocular adnexal lymphoma staging and treatment: American Joint Committee on Cancer versus Ann Arbor. *Eur J Ophthalmol*. 2013;23(3):344-355.
- Looi A, Gascoyne RD, Chhanabhai M, Connors JM, Rootman J, White VA. Mantle cell lymphoma in the ocular adnexal region. *Ophthalmology*. 2005;112(1):114-119.
- Hon C, Chan RT, Ma ES, Shek TW, Yau K, Au WY. Lymphomatous proptosis as a novel feature of mantle cell lymphoma. *Leuk Lymphoma*. 2006;47(1):71-75.
- Swerdlow SH, Campo E, Harris NL. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Vol 4. Lyon, France: IARC Press; 2008.
- Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res*. 1971;31(11):1860-1861.
- Amin MB, Edge S, Greene F, et al. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.
- Sniegowski MC, Roberts D, Bakhroum M, et al. Ocular adnexal lymphoma: validation of American Joint Committee on Cancer seventh edition staging guidelines. *Br J Ophthalmol*. 2014;98(9):1255-1260.
- Smith A, Howell D, Patmore R, Jack A, Roman E. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. *Br J Cancer*. 2011;105(11):1684-1692.
- Nieländer I, Martín-Subero JI, Wagner F, et al. Recurrent loss of the Y chromosome and homozygous deletions within the pseudoautosomal region 1: association with male predominance in mantle cell lymphoma. *Haematologica*. 2008;93(6):949-950.
- Pals ST, de Gorter DJ, Spaargaren M. Lymphoma dissemination: the other face of lymphocyte homing. *Blood*. 2007;110(9):3102-3111.

29. Grillo-López AJ, White CA, Dallaire BK, et al. Rituximab: the first monoclonal antibody approved for the treatment of lymphoma. *Curr Pharm Biotechnol.* 2000;1(1):1-9.
30. Munch-Petersen HD, Rasmussen PK, Coupland SE, et al. Ocular adnexal diffuse large B-cell lymphoma: a multicenter international study. *JAMA Ophthalmol.* 2015;133(2):165-173.
31. Rasmussen PK, Coupland SE, Finger PT, et al. Ocular adnexal follicular lymphoma: a multicenter international study. *JAMA Ophthalmol.* 2014;132(7):851-858.
32. Sjö LD, Heegaard S, Prause JU, Petersen BL, Pedersen S, Ralfkiaer E. Extranodal marginal zone lymphoma in the ocular region: clinical, immunophenotypical, and cytogenetical characteristics. *Invest Ophthalmol Vis Sci.* 2009;50(2):516-522.