

Original article

Lymphoma of the ocular adnexa: a retrospective study in a tertiary care center

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Background: Ocular adnexal lymphomas (OALs) are a heterogeneous group of lymphoid neoplasm, accounting for approximately 1-2% of nonHodgkin lymphomas and 8% of extranodal lymphomas. The incidence of tumors has continuously risen. This study aimed to describe the clinicopathologic and immunophenotypic features of OALs. **Material and methods:** Twenty-five OAL cases diagnosed in the Department of Pathology, Ramathibodi Hospital, between the years 2007 to 2018 were evaluated retrospectively in terms of clinical data and tumor types. Patient demographics, signs and symptoms, tumor location, stage of disease at diagnosis, and international prognostic index score (IPI score) were evaluated. Pathologic review of all cases was performed according to the WHO classification 4th edition. **Result:** The included population in this study was 25 cases with 60% males and a median age of 63 years. Three tumor subtypes, including extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue or MALT lymphoma (92%), small lymphocytic lymphoma (4%) and diffuse large B-cell lymphoma (4%), were identified in this study. The most involved site was the eyelid (48%), followed by the lacrimal gland (35%) and conjunctiva (13%). All cases exhibited a palpable mass on physical examination. Most patients had stage 1 disease on diagnosis with low IPI score and proper treatment outcome.

Keywords : ● Ocular adnexa ● Lymphoma ● Pathology ● Treatment outcome

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นิพนธ์ต้นฉบับ

มะเร็งต่อมน้ำเหลืองของอวัยวะเคียงลูกตา: การศึกษาย้อนหลังในศูนย์ดูแลตติยภูมิ

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บทคัดย่อ

โรคมะเร็งต่อมน้ำเหลืองของอวัยวะเคียงลูกตาเป็นกลุ่มเนื้องอกของอวัยวะน้ำเหลืองที่มีความหลากหลาย พบประมาณร้อยละ 1-2 ของโรคมะเร็งต่อมน้ำเหลืองทั้งหมดและประมาณ 8% ของโรคมะเร็งต่อมน้ำเหลืองที่เกิดนอกต่อมน้ำเหลือง (extranodal lymphoma) อุบัติการณ์ของโรคได้เพิ่มขึ้นอย่างต่อเนื่อง ผู้วิจัยมีวัตถุประสงค์เพื่อศึกษาประวัติทางคลินิกและพยาธิวิทยา รวมถึงการแสดงออกของโปรตีนของโรคมะเร็งต่อมน้ำเหลืองของอวัยวะเคียงลูกตา

การวิจัยเป็นการศึกษาย้อนหลังจากชิ้นเนื้อของผู้ป่วยโรคมะเร็งต่อมน้ำเหลืองของอวัยวะเคียงลูกตาที่ได้รับการวินิจฉัยและรักษาในโรงพยาบาลรามาธิบดีระหว่างปี พ.ศ. 2551-2561 ซึ่งผ่านเกณฑ์คัดเข้าและคัดออกรวม 25 ราย โดยศึกษาข้อมูลทางประชากร อาการและอาการแสดงทางคลินิก ตำแหน่งรอยโรค ระยะของโรคและค่า international prognostic index score (IPI score) รวมถึงการทบทวนพยาธิวิทยาของรอยโรคของผู้ป่วยทุกรายโดยอิงตาม WHO classification ฉบับพิมพ์ครั้งที่ 4

ผลการศึกษาจากผู้ป่วย 25 รายพบว่าผู้ป่วยเป็นเพศชายร้อยละ 60 มีค่ากลางของอายุอยู่ที่ 63 ปี ชนิดของมะเร็งที่พบได้แก่ extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue หรือ MALT lymphoma (92%), small lymphocytic lymphoma (4%), และ diffuse large B-cell lymphoma (4%) ตำแหน่งของโรคที่พบบ่อยคือเปลือกตา (48%) ตามด้วยต่อมน้ำตา (35%) และเยื่อぶตา (13%) การตรวจร่างกายพบก้อนในทุกราย ผู้ป่วยส่วนใหญ่ตรวจพบโรคในระยะที่หนึ่งและมีค่า IPI ต่ำ ผลการรักษาอยู่ในระดับดี

คำสำคัญ : ● อวัยวะเคียงลูกตา ● มะเร็งต่อมน้ำเหลือง ● พยาธิวิทยา ● ผลการรักษา

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2565;32:35-43.

Introduction

Ocular adnexal organs consist of the conjunctiva, eyelid, lacrimal gland and periorbital soft tissue. The ocular adnexal lymphomas comprise a heterogeneous group of lymphoid neoplasms, accounting for approximately 1 to 2% of nonHodgkin lymphomas and 8% of extranodal lymphomas.^{1,2} The majority are low-grade B-cell lymphomas, with extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue, or MALT lymphoma, being the most frequently encountered subtype.¹⁻⁷

OALs occurred among patients ranging in age from middle aged to elderly. Clinical manifestations include a salmon- pink patch on the conjunctiva, palpable mass, blurred vision, ptosis and a bulging eye.^{1,7} At presentation, most OALs were localized and had favorable outcomes.^{1,4} This study aimed to characterize the clinicopathologic and immunophenotypic characteristics of OALs.

Materials and Methods

The study employed a retrospective and descriptive design, recruiting all surgical pathology cases of ocular adnexal lymphomas diagnosed between 2007 and 2018

at Ramathibodi Hospital's Department of Pathology.

We included cases with available clinical information, paraffin-embedded tissue, and glass slides containing an adequate tissue sample. We excluded cases with no objective evidence of lymphoma, including light-chain restriction, abnormal CD43 expression or monoclonal gene rearrangement. The conjunctiva, eyelid, lacrimal gland and eyelid were all sampled. In all cases, hematoxylin and eosin sections were reviewed. Immunohistochemical staining of paraffin sections or flow cytometry was used to determine the immunophenotype. Two cases were studied molecularly to determine monoclonal gene rearrangement. Immunohistochemical staining was carried out using an automated immunostainer (Ventana BenchMark Ultra, Ventana BenchMark XT and Dako Autostainer Link 48). Immunohistochemical staining was performed at the time of biopsy, and panel compositions were changed over time. As a result, additional immunohistochemical staining was performed in the chosen case. Table 1 lists the antibodies and probes used in this study.

Table 1 Antibodies used for immunohistochemical study

Antibodies	Source	Dilution
CD3	Dako	1:100
CD5	Novocastra	1:100
CD20	Dako	1:1000
CD23	Novocastra	1:100
CD10	Novocastra	1:50
BCL2	Dako	1:1000
BCL6	Novocastra	1:100
Cyclin D1	Dako	Ready-to-use
CD43	Dako	1:100
Ki-67	Dako	1:100
Kappa light chain	Ventana	Ready-to-use
Lambda light chain	Ventana	Ready-to-use
IgG heavy chain	Dako	1:8000
IgA heavy chain	Ventana	Ready-to-use
IgM heavy chain	Dako	1:1000
CD21	Cell Marque	1:50
EBER	Ventana	Ready-to-use
MUM1	Dako	1:100

Flow cytometric analysis was performed using the BD LSR Fortessa with BD FACSDiva Software and BDCS&T beads for calibration. A 14-color analysis was performed using a blue laser, a red laser, a violet laser and a 355 UV laser. On a linear scale, forward and side scatter measurements were taken. Logarithmic scales were used to quantify immunofluorescence. BD Bioscience, Dako, Biolegend and Exbio provided the monoclonal antibodies used in this study. Light scattering with a CD45-positive gate was used to remove cellular debris and clumps.

Clinical data were extracted from the medical record in detail, including age, sex, signs and symptoms, location of involvement, laterality of disease, international prognostic index (IPI) score, stage at diagnosis, type of therapy and treatment outcome. All cases were classified using the revised WHO classification system, 4th edition.

Results

The population studied consisted of 25 individuals, 15 males (60%) and 10 females (40%). The median age of the population was 63 years (range 38-82 years). We identified three tumor subtypes: MALT lymphoma (92%), small lymphocytic lymphoma (4%) and diffuse large B-cell lymphoma (4%). Forty-eight percent of the tumors occurred in the eyelid, followed by the lacrimal gland (36%), conjunctiva (12%) and periorbital soft tissue (4%). The majority of cases (83%) showed unilateral organ involvement. The clinical presentation comprised swelling (63%), bulging eye (13%), irritation symptoms (13%) and blurred vision (4%). Eight percent of patients were asymptomatic and the lesions were discovered during radiologic evaluation for other illnesses. On physical examination, all cases presented palpable mass. At the time of diagnosis, 44% of cases were classified as stage I disease. Most cases (44%) had a low IPI score, followed by low intermediate and high intermediate scores. Chemotherapy, radiotherapy and a combination of the two were used as forms of therapy. Eighty-three percent of cases experienced complete remission. The

detailed patient demographics, signs and symptoms, stage at diagnosis, IPI score, types of therapy and clinical outcome are listed in Table 2.

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

Twenty-three cases were classified as MALT lymphoma. The patients totaled 14 males (61%) and 9 females (39%), 38-52 years old (median, 65). The lymphomas involved the eyelid (48%), lacrimal gland (35%), conjunctiva (13%) and periorbital soft tissue (4%). Eighty-two percent of cases entailed unilateral organ involvement. The histopathology revealed diffuse infiltration of small lymphoid cells with sparse to abundant pale cytoplasm. The nuclei were slightly irregular and chromatin was dispersed. Nucleoli were unnoticeable, and plasma cells were found in all cases. Sclerosis, residual follicle, polykaryocyte, Dutcher body and lymphoepithelial lesion were observed in 78, 52, 48, 30 and 9% of all cases, respectively (Figure 1, A-D). CD20 and BCL2 were expressed in all MALT lymphomas. They lacked CD3, CD5, CD10, BCL6 and cyclin D1 expression. Two cases (9%) were positive for CD23. Light-chain restriction was detected in 96% of cases, with kappa and lambda light-chain restriction occurring in 61 and 35% of cases, respectively. A case that lacked light-chain restriction exhibited aberrant CD43 expression. In 74% of cases, IgG, IgM and IgA heavy chains were restricted with IgG predominating (52%). Aberrant CD43 expression was demonstrated in 26% of cases. The Ki-67 proliferative index was less than 5 to 30%, with the proliferative index of 10% or less in 83% of cases (Figure 1, E-H).

Small lymphocytic lymphoma

One case of small lymphocytic lymphoma was identified in this study. This involved a 56-year-old-man presenting unilateral eyelid mass. At diagnosis the case had reached stage III due to lymph node involvement of both sides of the diaphragm. The IPI score and type of therapy were unavailable because the patient was referred to another hospital. The morphology showed diffuse small lymphoid proliferation with proliferation

Table 2 Demographic and clinical data

	EMZL (N = 23)	SLL (N = 1)	DLBCL (N = 1)	Total (N = 25)
Population	23 (92%)	1 (4%)	1 (4%)	25 (100%)
Age	38-82 (median 65)	56	52	38-82 (median 63)
Sex, male	14 (61%)	1	0	15 (60%)
Location				
Conjunctiva	3 (13%)	0	0	3 (12%)
Eyelid	11 (48%)	1	0	12 (48%)
Lacrimal gland	8 (35%)	0	1	9 (36%)
Periorbital soft tissue	1 (4%)	0	0	1 (4%)
Laterality				
Unilateral	18 (82%)	1	1	20 (83%)
Sign				
Swelling	13 (57%)	0	0	15 (63%)
Bulging eye	3 (13%)	0	0	3 (13%)
Blurred vision	1 (4%)	0	0	1 (4%)
Irritation symptom or tearing	3 (13%)	0	0	3 (13%)
No symptom	2 (9%)	0	0	2 (8%)
NA	1 (4%)			
Clinical feature				
Mass	23 (100%)	1	1	25 (100%)
Stage at diagnosis				
Stage I	11 (48%)	0	0	11 (44%)
Stage II	1 (4%)	0	0	1 (4%)
Stage III	2 (9%)	1	1	4 (16%)
Stage IV	3 (13%)	0	0	3 (12%)
NA	6 (26%)	0	0	6 (24%)
IPI score				
Low	11 (47.8%)	0	0	11 (44%)
Low intermediate	4 (17.4%)	0	1	5 (20%)
High intermediate	4 (17.4%)	0	0	4 (16%)
High	0 (0%)	0	0	0 (0%)
NA	4 (17.4%)	1	0	5 (20%)
Therapy				
Received therapy	18 (78%)	0	0	18 (72%)
Type of therapy				
Chemotherapy	5 (28%)	0	0	5 (28%)
Radiotherapy	6 (33%)	0	0	6 (33%)
Combined both	6 (33%)	0	0	6 (33%)
NA	1 (6%)	0	0	1 (6%)
Treatment outcome				
Complete remission	10 (83%)	0	0	10 (83%)
Progressive disease	0 (0%)	0	0	0 (0%)
Recurrence	2 (17%)	0	0	2 (17%)
In period of treatment	4	0	0	4
NA	2	0	0	2

EMZL: extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; SLL: small lymphocytic lymphoma;
DLBCL: diffuse large B-cell lymphoma

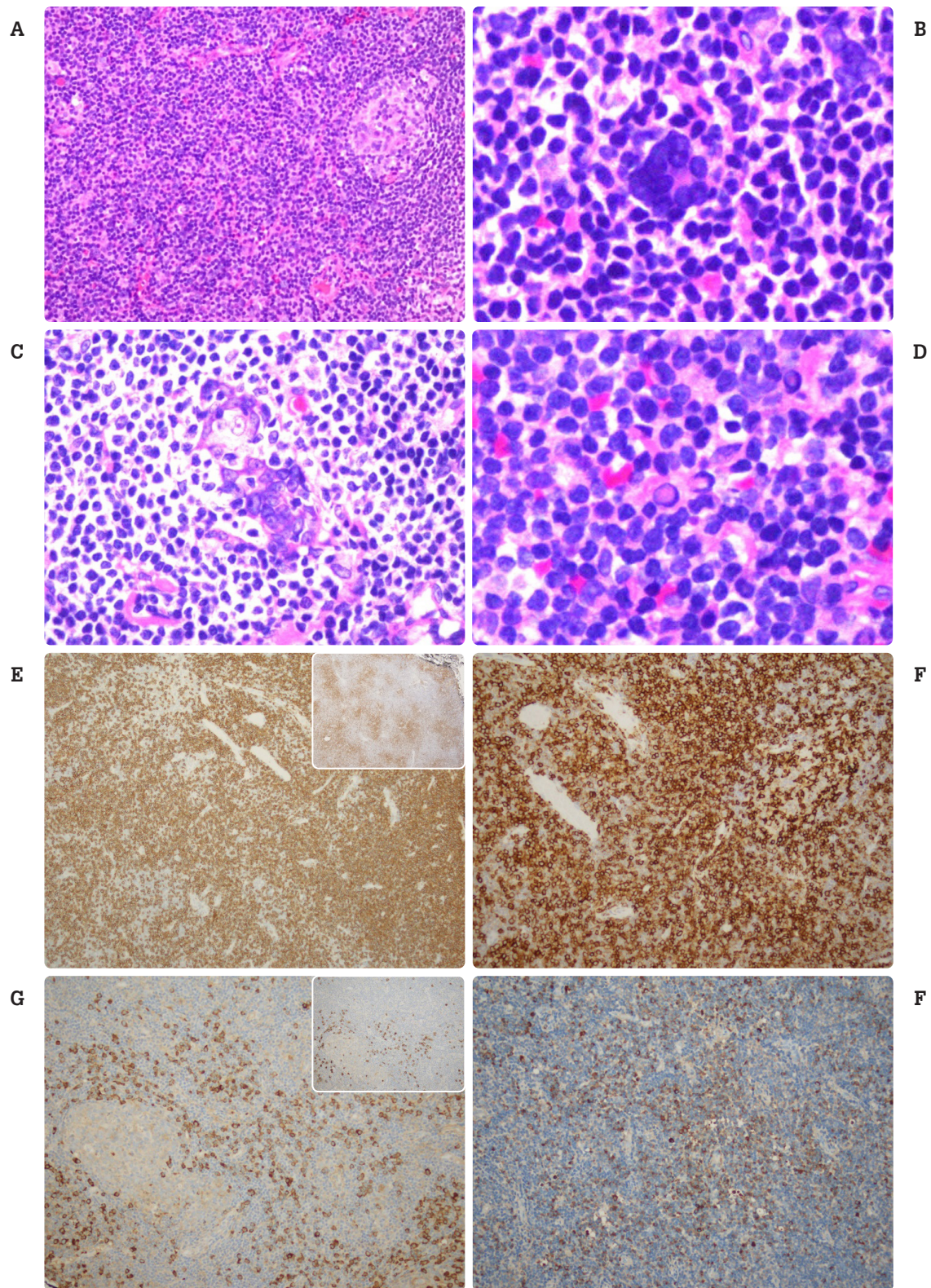


Figure 1: MALT lymphoma. A, Residual follicle and tumor (hematoxylin-eosin, original magnification x200). B, Polykaryocyte (hematoxylin-eosin, original magnification x600). C, Lymphoepithelial lesion (hematoxylin-eosin, original magnification x400). D, Dutcher bodies (hematoxylin-eosin, original magnification x600). E, CD20 expression (original magnification x100) and negative for CD3 (inset) (original magnification x100). F, CD43 aberrant expression (original magnification x200). G, Lambda-light chain restriction (original magnification x200) compared with kappa-light chain expression (inset) (original magnification x200). H, IgG-heavy chain restriction (original magnification x200)

centers (Figure 2). High-powered field examination demonstrated scattered paraimmunoblasts in the proliferation center areas. The immunophenotype revealed CD20 expression in conjunction with CD5 and CD23. BCL2 expression was also positive, whereas CD3, CD10, BCL6, CD43 and cyclin D1 expressions were negative. Evidence was found of kappa-light-chain and IgM-heavy-chain restriction. The Ki-67 proliferation index was approximately 25%.

Table 3 Morphology of MALT lymphoma

Histology	Result (N=23)
Diffuse pattern	23 (100%)
Plasma cell	23 (100%)
Sclerosis	18 (78%)
Reactive/residual follicle	12 (52%)
Dutcher body	7 (30%)

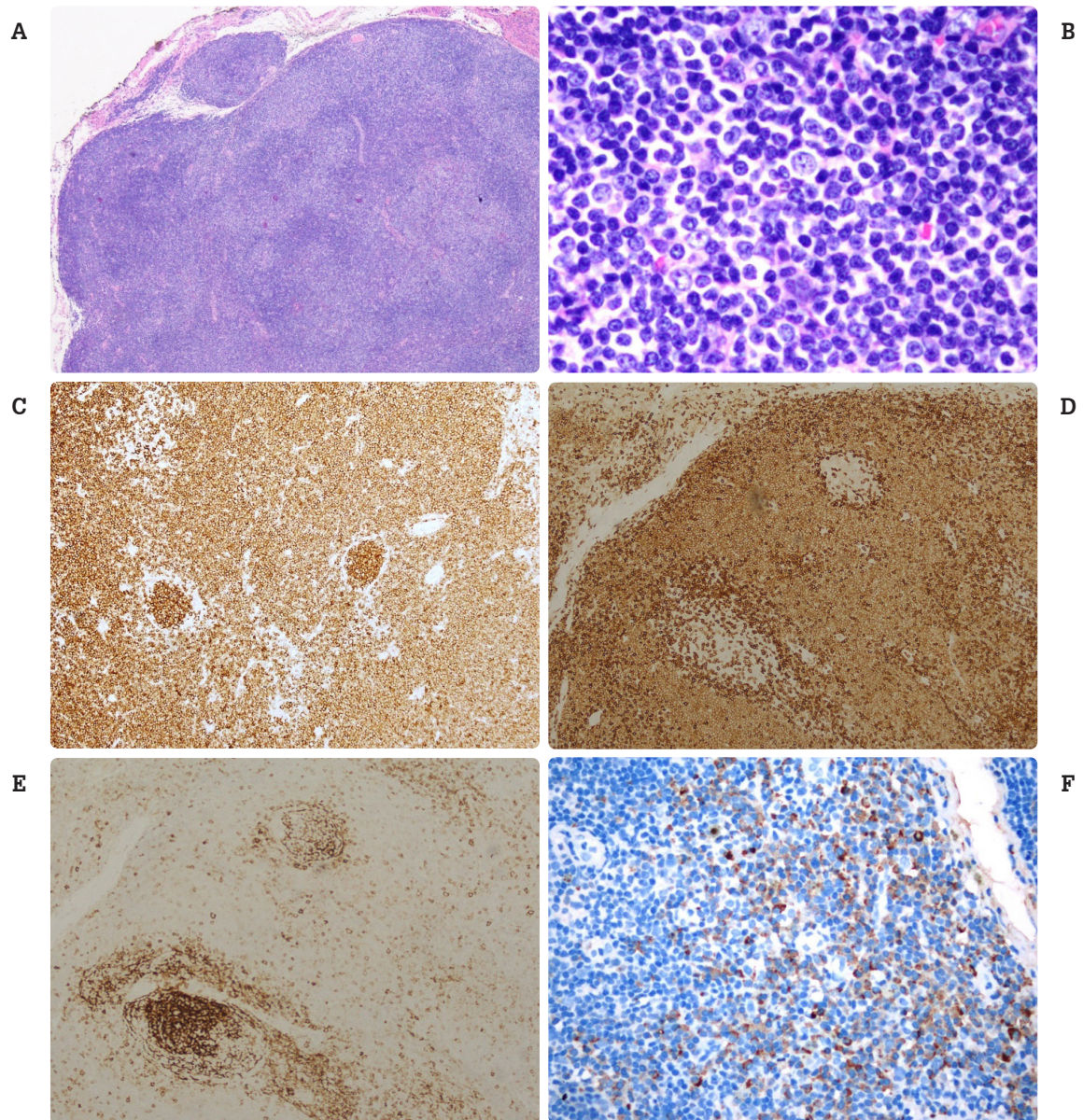


Figure 2: Small lymphocytic lymphoma. A, Diffuse small lymphoid proliferation with proliferation center (hematoxylin-eosin, original magnification x40). B, Paraimmunoblasts (hematoxylin-eosin, original magnification x400). C, CD20 expression of tumor and residual follicles (original magnification x100). D, CD5 expression (original magnification x100). E, CD23 expression of tumor cells (arrow) (original magnification x100). F, Kappa-light chain restriction (original magnification x200).

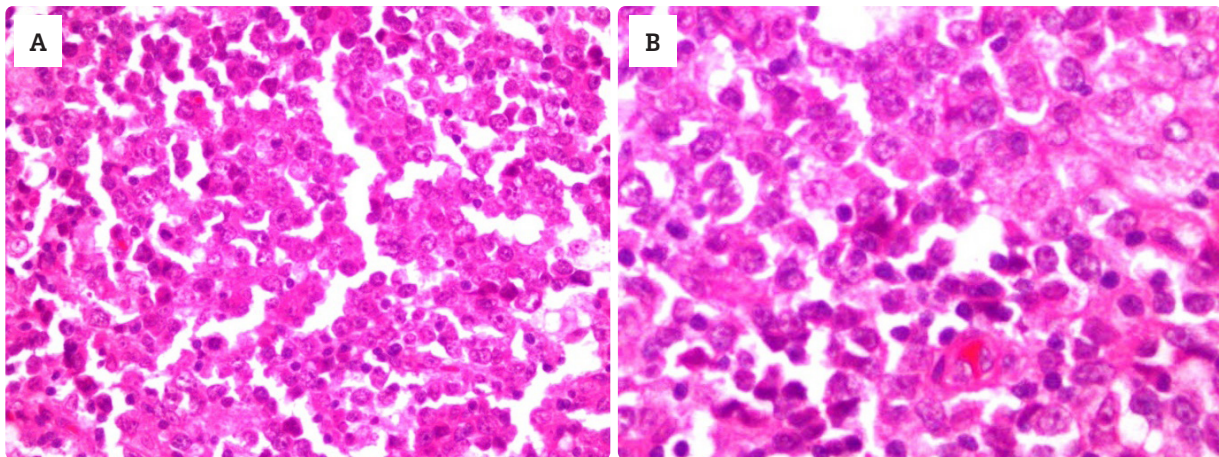


Figure 3 Diffuse large B-cell lymphoma. A, Diffuse infiltration of large-sized lymphoid cells (hematoxylin-eosin, original magnification x400). B, Centroblastic morphology of the tumor (hematoxylin-eosin, original magnification x600).

Diffuse large B-cell lymphoma

This study identified one case of diffuse large B-cell lymphoma in a 52-year-old woman. The clinical presentation was unilateral lacrimal gland mass. At the time of diagnosis, the patient was in stage III due to lymph node involvement of both sides of the diaphragm, and had a low-intermediate IPI score. The type of therapy was unavailable due to the patient's referral to another hospital. The morphology revealed diffuse infiltration of large, centroblastic lymphoid cells. They expressed CD20 and exhibited an immunophenotype resembling germinal center B cells (positive for CD10, BCL6 and MUM1). The Ki-67 proliferation index was approximately 90%.

Discussion

This study of ocular adnexal lymphomas found that the diseases occurred more frequently among older patients with a slight male preponderance. The eyelids and lacrimal glands were the two frequently involved sites accounting for over 80% of cases. All patients presented a mass lesion. All lymphomas in this study comprised B-cell lymphomas and the most frequently encountered lymphoma subtype was MALT lymphoma (92% of cases), which was low-grade and had a favorable prognosis. Almost one half of the patients received a

diagnosis of stage 1 disease and had a low IPI score. These results were similar to those of other series in terms of patient's age, most frequent tumor subtype, tumor stage and prognosis, although most series have reported a higher proportion of female patients^{1,4,6,7}. In other series^{1,4,6,7}, periorbital soft tissue was the most common site of tumor involvement, while our series found that the eyelid was the most frequently affected site.

Histopathologic and immunophenotypic features of MALT lymphoma were similar to those found in other sites. Interestingly, our series detected a high proportion of cases with sclerosis (78%), different from the related large series of Ferry et al. that identified only 20% of a total of 182 MALT lymphoma cases¹. The underlying causes associated with MALT lymphoma development in our study, such as autoimmune disease or *Chlamydia psittaci*¹, were unknown. Our patients presented no recorded history of autoimmune disease, and we did not investigate evidence of *C. psittaci* infection in this study as being beyond the scope of this study.

According to Ferry et al.¹, and McKelvie et al.⁴, studies, follicular lymphoma was the second most common type of lymphoma involving the ocular adnexa, accounting for 23 and 17% of cases, respectively. Other B-cell lymphomas, such as small lymphocytic lymphoma or diffuse large B-cell lymphoma, have infrequently affected

this area. Our series found no follicular lymphoma type and identified only one case of small lymphocytic lymphoma and one case of diffuse large B-cell lymphoma. Both lymphomas showed classic histopathology and immunophenotype similar to those found in other sites. The limitation of our series was the small sample size.

Our study reported types of lymphoma affecting the ocular adnexa, including the patient's clinical setting. The majority of cases involved low grade B-cell lymphomas and MALT lymphomas accounting for over 90% of all cases. The eyelid was the most frequently involved site. All cases presented a mass lesion. The majority of patients received a diagnosis with stage 1 disease, had a low IPI score and good treatment outcome. The generalizability of the results was limited by the small sample size. Further study for evidence of *C. psittaci* association may yield more information.

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