Int J Clin Exp Pathol 2018;11(3):1520-1528
www.ijcep.com /ISSN:1936-2625/IJCEP0069735

Original Article

Ocular adnexal mucosa-associated lymphoid tissue lymphoma: a single center experience of 32 patients from China

Yue Li[1*], Fang-Tian Wu[1*], Li Wang[1], Jin-Hua Liang[1], Hua-Yuan Zhu[1], Jia-Zhu Wu[1], Wei Wu[1], Yi Xia[1], Lei Fan[1], Hu Liu[2], Sheng Zhang[3], Zhi-Hong Zhang[4], Jian-Yong Li[1], Wei Xu[1]

[1]Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Collaborative Innovation Center for Cancer Personalized Medicine, Nanjing Medical University, Nanjing, China; Departments of [2]Ophthalmology, [3]Radiology, [4]Pathology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China. [*]Equal contributors.

Received November 24, 2017; Accepted January 19, 2018; Epub March 1, 2018; Published March 15, 2018

Abstract: MALT represents the most common subtype in ocular adnexa lymphoma. Little data, however, has been reported in China. We consecutively analyzed 32 patients from April 2008 to January 2016. Median age at diagnosis was 57 (32-90) years. Most patients presented with stage IE (30/32, 87.5%) and the remaining 2 staged IVE. Treatment and followup data were available for 29 patients. Other than resection and biopsy for diagnosis, most of them (20/29, 68.9%) received radiotherapy. The rest underwent chemotherapy (1, 3.5%), both radiotherapy and chemotherapy (2, 6.9%), or 'watch and wait' (6, 20.7%). With a median followup of 28 (6-94) months, all of the patients are alive. Two cases progressed at 24 months and 30 months. Comparing the PFS for four treatment arms, no significant difference can be observed (P=0.147). Our data demonstrated the chronic clinical course and excellent prognosis of OAML. For localized cases, surgery combined with radiotherapy is recommended.

Keywords: Prognosis, ocular adnexal mucosa-associated lymphoid tissue lymphoma, treatment

Introduction

Lymphoma is the most common subtype of malignancy among ocular adnexa malignancies. It can involve conjunctiva, lacrimal gland, orbit, eyelids, and orbital muscles. Ocular adnexa lymphoma (OAL) was reported for the first time in 1952 by Feinstein and Krause [1]. The incidence of OAL was described as 0.18-0.31 per 100,000 per year in the 1970s [2] and it has increased gradually in the last forty years [3].

The histology of OALs are mostly of low-grade (84%) with only 16% high-grade [4]. Ocular adnexa MALT lymphoma (OAML) is the most common subtype of OAL and others less common include diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), lymphoplasmacytic lymphoma (LPL), and mantle cell lymphoma (MCL) [5-7].

However, little data about OAML cohorts have been reported in China. Thus, we consecutively analyzed 32 OAML cases diagnosed and treated in our hospital to assess their clinical characteristic, treatment and outcomes.

Material and methods

Patient selection and diagnosis

Thirty-two OAML cases diagnosed and treated in our hospital from April 2008 to January 2016 were enrolled in our research. All of them were provided informed consent for our institutional guidelines at their first visit, according to the 1975 guidelines of the Declaration of Helsinki.

Data of patient gender, age, Ann Arbor stage, ECOG performance status, serum lactate dehydrogenase (LDH), the number of extra nodal sites involved (ESI), β2-microglobulin (β2-MG), serum ferritin (SF), serum paraprotein, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and virus (EBV/HBV) status were

Table 1. Characteristics of OAML patients at diagnosis and first-line therapy

		Number of patients	Proportion
Gender	Male	21	65.6%
	Female	11	34.4%
Age	Median/Range	57 (32-90)	
Involved sites	Conjunctiva	3	9.4%
	Lacrimal gland	2	6.3%
	Orbit	15	46.8%
	Eyelid	10	31.2%
	Orbital muscles	2	6.3%
Stage	IE	30	93.8%
	IVE	2	6.2%
ECOG	0	31	96.8%
	≥1	1	3.2%
LDH	Normal	31	96.8%
	Over ULN	1	3.2%
IPI	0-1	30	93.8%
	>1	2	6.2%
First-line therapy (n=29)	Surgery	6	20.7%
	Surgery/Radiotherapy	20	68.9%
	Surgery/Chemotherapy	1	3.5%
	Surgery/Chemotherapy/Radiotherapy	2	6.9%

IPI = International Prognosis Index; ECOG = Eastern Cooperative. Oncology Group; LDH = lactate dehydrogenase.

collected. The International Prognostic Index (IPI) was used for prognostic stratification. All of the patients underwent bone marrow aspiration and radiological scanning of not only orbit, but also the whole body.

Histological diagnosis of all of the patients with OAML was performed, according to the World Health Organization classification for hematologic and lymphoid tissues tumors (2008 version), by reference pathologists.

Statistical analysis

The statistical analyses were performed using the SPSS software (version 18.0) and Graphpad Prism 6. Chi square-test was used to test association between two categorical variables. Progression-free survival (PFS) was defined as the period from the date of diagnosis of OAML to disease progression after the first treatment or to the last followup date. Overall survival (OS) was defined as the period from diagnosis to the date of last followup or death. We used the Kaplan-Meier curve to describe PFS and OS and log-rank analysis to test the differences.

Results

Baseline clinical characteristics

Thirty-two patients with histologically verified OAML who were diagnosed and treated at our center between April 2008 to January 2016 were enrolled in this study. As shown in **Table 1**, the median age at diagnosis was 57 years (range, 32-90 years) with a male predominance (male/female, 21/22). The median followup time was 28 months (range, 6-94 months).

OAML usually presented with asymptomatic ocular adnexal mass and ophthalmologists practiced biopsy or surgical excision to confirm the diagnosis. Typical histological changes and immunophenotypic finding of the tumors is CD20 (+), PAX5 (+), BCL-2 (+), CD3 (-), CD5 (-), CD10 (-), BCL-6 (-), CCND-1 (-), and Ki-67< 10%, as shown in **Figure 1**. Most common site of OAML was orbit (15/32, 46.8%), followed by eyelid (10/32, 31.2%), conjunctiva (3/32, 9.4%), lacrimal gland (2/32, 6.3%), and orbital muscles (2/32, 6.3%). Most of the patients had localized disease, that is, stage IE according to

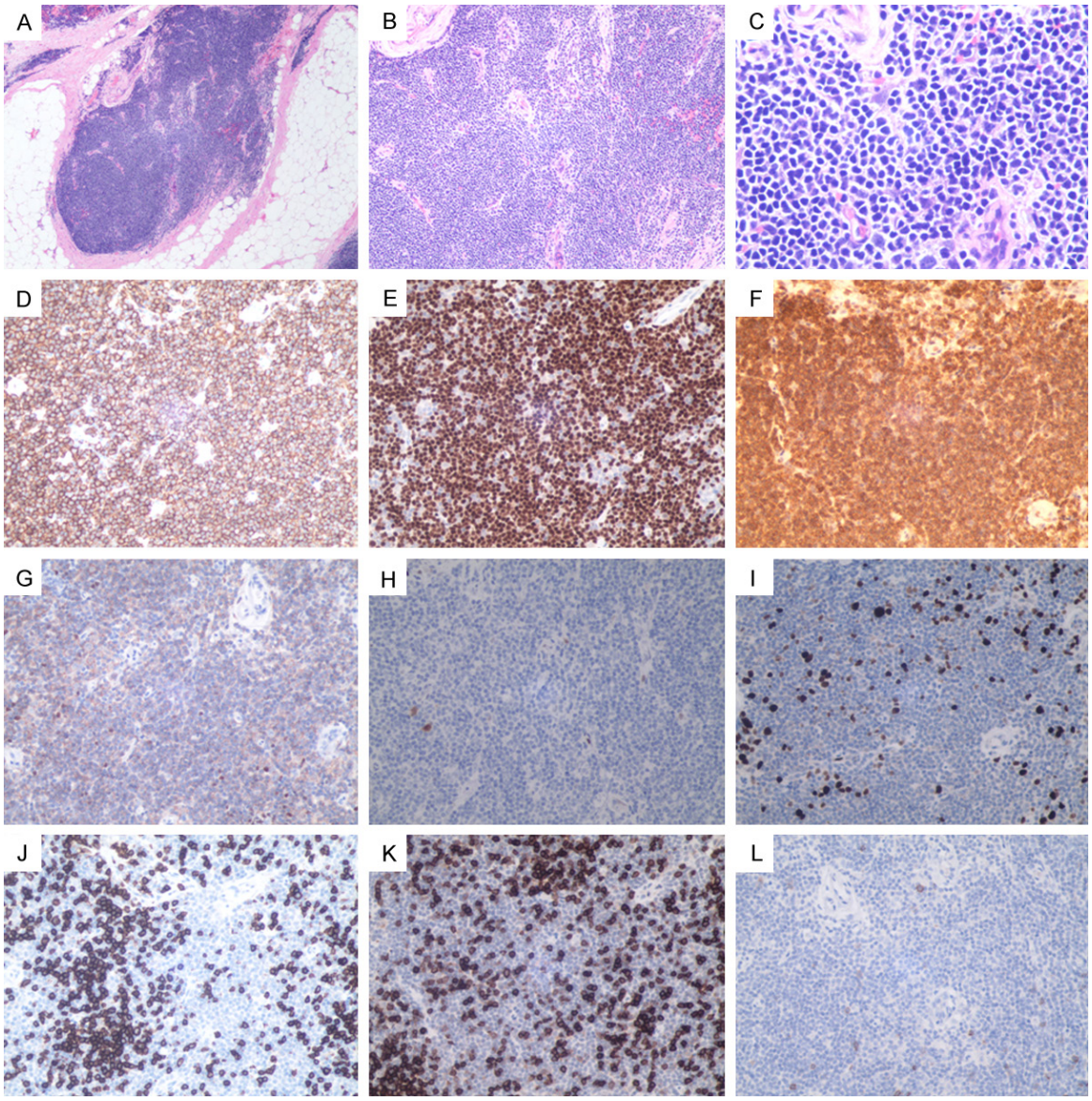

Figure 1. Typical histological changes and immunophenotypic findings of OAML. (A) Hematoxylin and eosin, × 40; (B) Hematoxylin and eosin, × 100; (C) Hematoxylin and eosin, × 400. Staining with an immunohistochemical marker of (D) CD20 (original magnification × 200); (E) PAX-5 (original magnification × 200); (F) BCL-2 (original magnification × 200); (G) BCL-6 (original magnification × 200); (H) CCND-1 (original magnification × 200); (I) Ki-67 (original magnification × 00); (J) CD30 (original magnification × 200); (K) CD5 (original magnification × 200); (L) CD10 (original magnification × 200).

Ann Arbor (30/32, 93.7%). Two (6.3%) presented with stage IVE, due to bone marrow involvement. Bone biopsy and immunohistochemistry (IHC) of patient No.11 was: CD5-, CD10-, CD20+, PAX5+, CD23-, BCL-2 weakly positive, and B-cell lymphoma bone marrow invasion. Bone marrow flow cytometry of patient No.14: atypical lymphocytes were positive for CD19 and CD20; negative for CD5, CD10, and CD23. CD19 positive cells expressed lambda light chain restriction. B symptoms were observed in only one case. During followup, no central nervous system involvement was found.

The International Prognostic Index (IPI) was available in all 32 patients and 30 of them (93.8%) were at low risk (IPI 0-1). Thirty-one (96.8%) patients were rated zero for European Cooperative Oncology Group (ECOG) performance status at diagnosis. Beta 2-MG level was measured in 29/32 patients and was elevated in 17.2% (5/29). SF was increased in

Table 2. Characteristics, treatment, and survival of OAML patients

No	Gender	Age	Localization	Ann arbor Stage	AJCC TNM stage	1st-line treatment	Chemotherapy (first-line)	Progression	PFS (months)	OS (months)	Alive
1	M	46	Orbit	IE	T2NXM0	Surgery/Radiotherapy		N	81.77	81.77	Y
2	F	60	Orbit	IE	T2NXM0	-		-		-	-
3	F	65	Lacrimal gland	IE	T1NXM0	-		-		-	-
4	M	90	Eyelid	IE	T3NXM0	Surgery		Y	24.5	43.77	Y
5	M	60	Orbit	IE	T2NXM0	Surgery		N	68.43	68.43	Y
6	F	58	Eyelid	IE	T3NXM0	Surgery/Radiotherapy		N	58.83	58.83	Y
7	M	69	Orbit	IE	T2NXM0	Surgery/Radiotherapy		N	58.13	58.13	Y
8	M	53	Conjunctiva	IE	T1NXM0	Surgery/Radiotherapy		N	56.8	56.8	Y
9	M	57	Orbit	IE	T2NXM0	-		-		-	-
10	M	63	Eyelid	IE	T3NXM0	Surgery		N	54.6	54.6	Y
11	F	55	Orbit	IVE	T2NXM1	Surgery/Chemoimmunotherapy/Radiotherapy	R-CHOP*4	N	42.1	42.1	Y
12	F	52	Eyelid	IE	T3NXM0	Surgery/Radiotherapy		N	42.07	42.07	Y
13	F	50	Orbit	IE	T2NXM0	Surgery		N	41.77	41.77	Y
14	M	74	Eyelid	IVE	T3NXM1	Surgery/Chemotherapy	miniCHOP*6	N	28.3	28.3	Y
15	M	78	Orbit	IE	T2NXM0	Surgery/Radiotherapy		N	27.67	27.67	Y
16	M	42	Orbit	IE	T2NXM0	Surgery/Chemotherapy/Radiotherapy	CHOP*3	N	26	26	Y
17	F	44	Eyelid	IE	T3NXM0	Surgery/Radiotherapy		N	26.47	26.47	Y
18	F	52	Oorbit	IE	T2NXM0	Surgery/Radiotherapy		N	16	16	Y
19	M	63	Orbit	IE	T2NXM0	Surgery		N	15.73	15.73	Y
20	M	55	Orbit	IE	T2NXM0	Surgery/Radiotherapy		N	12.67	12.67	Y
21	F	40	Orbital muscles	IE	T2NXM0	Surgery/Radiotherapy		N	27.07	27.07	Y
22	F	69	Orbital muscles	IE	T2NXM0	Surgery/Radiotherapy		N	20.33	20.33	Y
23	M	61	Eyelid	IE	T3NXM0	Surgery		Y	30.47	100.43	Y
24	M	57	Orbit	IE	T2NXM0	Surgery/Radiotherapy		N	17.3	17.3	Y
25	M	52	Eyelid	IE	T3NXM0	Surgery/Radiotherapy		N	12.47	12.47	Y
26	M	66	Lacrimal gland	IE	T1NXM0	Surgery/Radiotherapy		N	6.33	6.33	Y
27	M	48	Orbit	IE	T2NXM0	Surgery/Radiotherapy		N	30.3	30.3	Y
28	M	60	Eyelid	IE	T3NXM0	Surgery/Radiotherapy		N	25.97	25.97	Y
29	F	63	Orbit	IE	T2NXM0	Surgery/Radiotherapy		N	17.6	17.6	Y
30	M	63	Conjunctiva	IE	T1NXM0	Surgery/Radiotherapy		N	6.07	6.07	Y
31	F	32	Conjunctiva	IE	T1NXM0	Surgery/Radiotherapy		N	7.5	7.5	Y
32	M	53	Eyelid	IE	T3NXM0	Surgery/Radiotherapy`		N	6.83	6.83	Y

17.9% (5/28), ESR (erythrocyte sedimentation rate) in 25.0% (7/28), LDH (lactate dehydrogenase) in 3.2% (1/32), and CRP (C-reactive protein) in 10.7% (3/28). EBV-DNA copy numbers were available in 22 patients and 1 of them (4.55%) was over the upper limits of normal (5000 copy number). HBsAg was positive in 9.4% (3/32). No evidence of hepatitis C infection was found (0/32). Thyroid function test was performed on 16 patients. Three had abnormalities but no one could meet the diagnostic criteria of Grave's disease or chronic autoimmune thyroiditis (Hashimoto's thyroiditis). cANCA/pANCA/PR3-cANCA/MPO-ANCA were performed on 11 patients and all of them were negative. We also had paraprotein tested in 30 patients. IgM was elevated in 10/30 (33.3%), IgA in 3/30 (10%), and IgG in 1/30 (3.3%).

Treatment and outcomes

Different types of treatment were practiced on OAML patients and treatment details were available in 29 of 32 patients. Treatment details and brief clinical characteristics of patients are shown in **Table 2**. After diagnosis, 20 of 21 (68.9%) patients received radiotherapy, 1/29 (3.4%) patients were given chemotherapy, and 2/29 (6.9%) received both radiotherapy and chemo-immunotherapy/chemotherapy. The remaining six (20.7%) did not undergo any further treatment besides surgery and decided to watch and wait.

The majority of the patients (20/29, 68.9%) received local treatment which included both surgical resection and radiotherapy. All of them responded well and none progressed during followup. The total radiation dose ranged from 30 Gy to 55 Gy, mostly 34 Gy/17 f. Complications of radiotherapy included vision loss (1/20, 5.0%), dry eye syndrome (2/20, 10.0%), and cataracts (1/20, 5.0%). No other complications, such as keratitis and retinopathy, were observed.

A total of 6 (20.7%) patients were followed up without any further treatment. One patient with stage IE was diagnosed with left eye lesion (patient No.23). Thirty months after surgical resection, his eye lesion recurred. Moreover, a mass on his right eye was observed and also histologically diagnosed OAML. Considering his bilateral involvement, 6 cycles of CHOP (cyclophosphamide 1.2 g d1, epirubicin 80 mg d1, vincristine 2 mg d1, prednisone 50 mg bid d1-5) were administered and partial remission (PR) was achieved. The patient then received second-line chemo-immunotherapy of GDP (gemcitabine 1.6 g d1 d8, cis-Dichlorodiamineplatinum 100 mg d1, dexamethasone: 40 mg d1-4) for 4 cycles. With his lymph nodes and the eye lesion remaining in PR, he refused to take any further treatment. No progression had been observed until the end of our followup. One 90-year-old patient with stage IE was progressed 24 months after surgery. Considering his personal status, age, and history of prostate cancer we did not conduct any further therapy. Until the last followup, his eye lesion had been growing slowly and no evidence of other organ involvement had been observed.

One of the 29 (3.4%) patients received surgery and chemotherapy (patient No.14). This patient staged IVE received 6 cycles of mini CHOP (cyclophosphamide 0.7 g d1, epirubicin 60 mg d1, vincristine 1 mg d1, prednisone 35 mg bid d1-5). After the first-line treatment, PR was achieved and the patient refused to take further therapy. No progression had been observed until the end of our followup.

Two (6.9%) patients underwent surgery, radiotherapy and chemoimmunotherapy/chemotherapy. One was a 55 year old woman staged IVE (patient No.11). After surgical resection, she received chemoimmunotherapy (R-CHOP for 4 cycles: Rituximab 500 mg d0, cyclophosphamide 1.1 g d1, epirubicin 80 mg d1, vindesine 4 mg d1, prednisone 45 mg bid d1-5). Imaging assessment demonstrated PR of her eye lesion and then she received radiotherapy for 32 Gy/17 f. The other patient received CHOP (cyclophosphamide 1.4 g d1, epirubicin 90 mg d1, vincristine 2 mg d1, prednisone 50 mg bid d1-5) for 3 cycles and radiotherapy for 34.2 Gy/19 f (patient No.16). No progression was observed for both of them during our followup.

Up to our followup point, all of the 29 patients were alive with 100% of 3-years OS rate. Two patients progressed at 24 and 30 months after diagnosis, respectively, and the 3 year PFS rate was 85.0% (**Figure 2**). Comparing four treatment arms, no significant difference could be observed in PFS (P=0.147) (**Figure 3**).

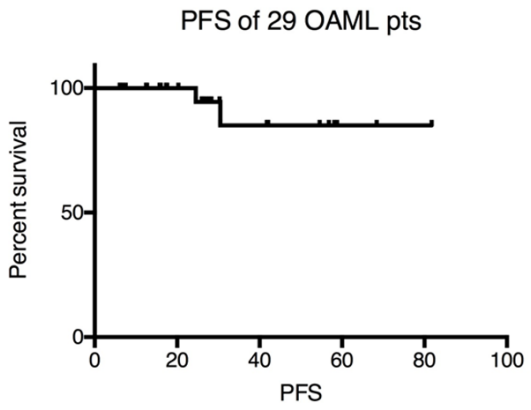

Figure 2. Kaplan-Meier curve for progression free survival of OAML patients.

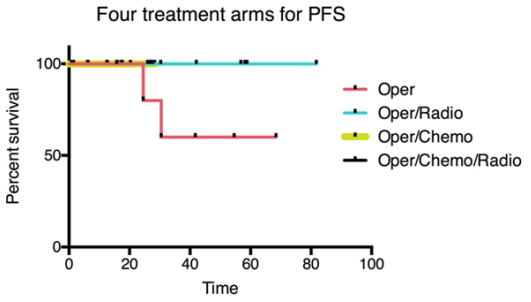

Figure 3. Kaplan-Meier curve for progression free survival of OAML patients in four treatment arms.

Discussion

MALT lymphoma can involve salivary glands, the gastrointestinal tract, bladder, and pulmonary. Ocular adnexa are one of the most common sites where MALT lymphoma can occur. We reported a series of 32 patients with OAML, comprising a relatively large cohort of OAML in China to date.

According to researchers from Korea and Japan, OAML presents at a median age of 45 years old at diagnosis and has a male preponderance [8-10]. However, reports from western countries including the United States and Italy, show an older age (median age, ~65 years) and a female preponderance (M/F= 1/1.5) [11-13]. The data of our series is quite consistent with those from Korea and Japan that males make up the majority, while the median age of diagnosis is older (57 years) but still younger than the western population. It has been demonstrated that the predilection age and gender constitution of OAML may have regional variation but Asians share some similarities. Unilateral involvement is more common than bilateral. According to Tan moto [14], Decaudin [15], and Ferry [16] the proportion of bilateral cases is no more than 25%. In our cohort, no bilateral involvement was observed at diagnosis. Orbit was reported to be the most common involved site among OAML, which is also confirmed in our data. Most of the patients had local disease, usually staged IE (Ann Arbor Staging system), and IPI score was mostly at low risk. This is also confirmed in our cohort. Two patients staged IVE had bone marrow involvement at first visit which may imply that bone marrow biopsy should be a routine test for patients with OAML.

It has been frequently reported that MALT lymphoma is usually accompanied by autoimmune disorders [17, 18]. Thyroid function test and ANCA series test (including cANCA/pANCA/PR3-cANCA/MPO-ANCA) were conducted in part of our cases. Three of 16 had abnormal thyroid function (lower T3/lower TG/higher A-TG and anti-T). According to a reference endocrinologist, none of them can be diagnosed with Grave's disease or chronic autoimmune thyroiditis (Hashimoto's thyroiditis). Among the 11 patients who had ANCA series test, the results were negative. In our series, OAML does not seem to be related to autoimmune disorders. However, more than a half of our cohort did not take these lab tests, thus more data are still needed to demonstrate the relationship between OAML and autoimmune disorders. Other risk factors evaluated, such as elevated β2-MG, TK1, ESR, CRP, SF, CA125, presence of paraproteinemia, also did not have prognosis significance in our cohort.

In order to reduce possible impairment of vision, the management of OAML requires a multidisciplinary cooperation which involves an ophthalmologist, hematologist, radiotherapist, and pathologist. Currently, treatments often applied for OAML patients include: surgery, radiotherapy, chemoimmunotherapy, and the 'watch and wait' strategy. In our center, patients with OAML are usually diagnosed in the Department of Ophthalmology via biopsy or resection. Subsequently, experienced hematologists will conduct an overall examination to assess the stage, prognosis, and to ma-

ke a precision treatment protocol. According to certain protocol, patients will be transferred to the corresponding department (hematology or radiology). However, sometimes the protocol cannot be implemented thoroughly due to poor patient compliance.

Before any treatment, a surgical resection or biopsy of the eye lesion is of great importance. Doctors can conduct more precise management after pathological and immunophenotyping analysis. However, *in situ* or disseminated extra ocular relapse occurs in the surgery group more frequently than the radiotherapy group [19, 20]. Thus, among the clinical course of OAML, the role of surgery is more likely to biopsy and figure out the diagnosis. In our series, six patients only received surgical resection as first-line therapy. Two of them (66.7%) relapsed at 24 and 40 months after diagnosis, respectively. Obviously, subsequent treatment after surgery is quite necessary incase of relapse.

For localized MALT lymphoma, radiotherapy is recognized as the most common management and a safe and effective treatment. Radiotherapy is reported to contribute to a local control rate of 100% and relapse rate ranging between 0%-15% [21-24]. However, radiotherapy is known not only for its high local control ratebut also for complications such as cataracts, keratitis, dry eye syndrome, and retinopathy [25-29]. In our cohorts, four cases in the radiotherapy group presented with complications after radiotherapy (one for amblyopia, two for dry eye syndrome, and the other for cataracts). All of these four cases reported that complications after radiotherapy did not affect their daily life. Recent reports have emphasized the importance of using a lead shield to protect the cornea during radiotherapy. With adequate protection, it seems that complications of radiotherapy are acceptable and manageable.

It was reported in the study by Avilés et al. that OAML patients did not benefit from the adjunct of chemoimmunotherapy to radiotherapy and the toxicities rates wassimilar in two treatment arms [30]. Another study illustrated that patients treated with radiotherapy with single reagent chemotherapy/immunotherapy and combination chemo-immunotherapy did not differ in OS rates [19]. In our center, chemo-immunotherapyis usually applied for OAML patients with systemic involvement. Radiotherapy will be added when complete remission of the eye lesion was not achieved.

For early stage OAML patients who do not receive treatment, survival rate is similar to those immediately treated. Tanimoto et al. conducted a study including 36 localized OAML cases [31]. At a median followup of 7 years, almost 70% patients did not require treatment. Forty-seven percent of patients progressed and 6% died because of progressive lymphoma. Thus, in the management of elderly and frail patients with resected lesions or asymptomatic disease, the 'watch and wait' strategy is strongly recommended.

There are some limitations of our series. OAL is a rare disease, likely representing as many as 8% of all extra nodal NHLs [2]. Its incidence is approximately 0.2 per 100,000 which makes it reasonable that, even though MALT lymphoma is the most common subtype of malignant lymphoma in the orbit, the incidence of OAML is quite low. Even taking this into account, our cohort is relatively small. Moreover, for indolent lymphoma, the followup time is relatively short to illustrate the prognosis precisely. It has been well demonstrated that H.pylori plays a vital role in the development of gastric MALT lymphoma. The relationship between C. psittaci and OAML is quite controversial and confusing. In 2004, Ferreri et al. first reported the presence of C.psittaci in 80% of OAML biopsies and doxycycline treatment led to positive remission of eye lesions in more than half the patients [32]. Yoo C et al., from Korea, also successfully isolated C.psittaci in approximately 80% of OAML patients [33]. Nevertheless, some research from Germany, China, Japan, USA, Cuba, Netherlands and France reported that no relationship was observed between C.psittaci and OAML [12, 34-38]. Thus, there appears to be a strong regional variability in the association of C.psittaci and OAML. As a limiting condition, the test of C.psittaci has not been conducted in our center. Further future research is still needed for the field of chlamydia-lymphoma associations.

Taken together, OAML is a relatively rare subtype of non-Hodgkin lymphoma with localized and indolent clinical course, although a fraction of them slowly progressed. Our data illustrates

the excellent prognosis of OAML despite various arms. Future investigations on OAML, especially prospective ones with long followingup time, are needed.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (30971296, 81170485, 81170488, 81370657, and 81470328), Project of National Key Clinical Specialty, the National Science & Technology Pillar Program (2014BAI09B12), and a project funded by Jiangsu Provincial Special Program of Medical Science (BL2014086).

Disclosure of conflict of interest

None.

Address correspondence to: Drs. Wei Xu and Jian-Yong Li, Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing 210029, China. Tel: +86-25-83781120; Fax: +86-25-83781120; E-mail: xuwei10000@hotmail.com (WX); lijianyong-lm@medmail.com.cn (JYL)

References

[1] Feinstein AR and Krause AC. Ocular involvement in lymphomatous disease. AMA Arch Ophthalmol 1952; 48: 328-337.

[2] Freeman C, Berg JW and Cutler SJ. Occurrence and prognosis of extranodal lymphomas. Cancer 1972; 29: 252-260.

[3] Moslehi R, Devesa SS, Schairer C and Fraumeni JF Jr. Rapidly increasing incidence of ocular non-hodgkin lymphoma. J Natl Cancer Inst 2006; 98: 936-939.

[4] Bessell EM, Henk JM, Wright JE and Whitelocke RA. Orbital and conjunctival lymphoma treatment and prognosis. Radiother Oncol 1988; 13: 237-244.

[5] Vali Khojeini E, Durham BH and Chen M. Mantle cell lymphoma and involvement of the orbit and ocular adnexa. Case Rep Pathol 2013; 2013: 581856.

[6] Coupland SE, Krause L, Delecluse HJ, Anagnostopoulos I, Foss HD, Hummel M, Bornfeld N, Lee WR and Stein H. Lymphoproliferative lesions of the ocular adnexa. Analysis of 112 cases. Ophthalmology 1998; 105: 1430-1441.

[7] Nola M, Lukenda A, Bollmann M, Kalauz M, Petrovecki M and Bollmann R. Outcome and prognostic factors in ocular adnexal lymphoma. Croat Med J 2004; 45: 328-332.

[8] Cho EY, Han JJ, Ree HJ, Ko YH, Kang YK, Ahn HS, Ahn SD, Park CJ and Huh J. Clinicopathologic analysis of ocular adnexal lymphomas: extranodal marginal zone b-cell lymphoma constitutes the vast majority of ocular lymphomas among Koreans and affects younger patients. Am J Hematol 2003; 73: 87-96.

[9] Mannami T, Yoshino T, Oshima K, Takase S, Kondo E, Ohara N, Nakagawa H, Ohtsuki H, Harada M and Akagi T. Clinical, histopathological, and immunogenetic analysis of ocular adnexal lymphoproliferative disorders: characterization of MALT lymphoma and reactive lymphoid hyperplasia. Mod Pathol 2001; 14: 641-649.

[10] Woo JM, Tang CK, Rho MS, Lee JH, Kwon HC and Ahn HB. The clinical characteristics and treatment results of ocular adnexal lymphoma. Korean J Ophthalmol 2006; 20: 7-12.

[11] Ferreri AJ, Dolcetti R, Du MQ, Doglioni C, Resti AG, Politi LS, De Conciliis C, Radford J, Bertoni F, Zucca E, Cavalli F and Ponzoni M. Ocular adnexal MALT lymphoma: an intriguing model for antigen-driven lymphomagenesis and microbial-targeted therapy. Ann Oncol 2008; 19: 835-846.

[12] Rosado MF, Byrne GE Jr, Ding F, Fields KA, Ruiz P, Dubovy SR, Walker GR, Markoe A and Lossos IS. Ocular adnexal lymphoma: a clinicopathologic study of a large cohort of patients with no evidence for an association with Chlamydia psittaci. Blood 2006; 107: 467-472.

[13] Fung CY, Tarbell NJ, Lucarelli MJ, Goldberg SI, Linggood RM, Harris NL and Ferry JA. Ocular adnexal lymphoma: clinical behavior of distinct world health organization classification subtypes. Int J Radiat Oncol Biol Phys 2003; 57: 1382-1391.

[14] Tanimoto K, Kaneko A, Suzuki S, Sekiguchi N, Watanabe T, Kobayashi Y, Kagami Y, Maeshima AM, Matsuno Y and Tobinai K. Primary ocular adnexal MALT lymphoma: a long-term follow-up study of 114 patients. Jpn J Clin Oncol 2007; 37: 337-344.

[15] Decaudin D, de Cremoux P, Vincent-Salomon A, Dendale R and Rouic LL. Ocular adnexal lymphoma: a review of clinicopathologic features and treatment options. Blood 2006; 108: 1451-1460.

[16] Ferry JA, Fung CY, Zukerberg L, Lucarelli MJ, Hasserjian RP, Preffer FI and Harris NL. Lymphoma of the ocular adnexa: a study of 353 cases. Am J Surg Pathol 2007; 31: 170-184.

[17] Wohrer S, Troch M, Streubel B, Zwerina J, Skrabs C, Formanek M, Hauff W, Hoffmann M, Mullauer L, Chott A and Raderer M. MALT lymphoma in patients with autoimmune diseases: a comparative analysis of characteristics and clinical course. Leukemia 2007; 21: 1812-1818.

[18] Nutting CM, Shah-Desai S, Rose GE, Norton AP and Plowman PN. Thyroid orbitopathy possibly predisposes to lateonset of periocular lymphoma. Eye (Lond) 2006; 20: 645-648.
[19] Sasai K, Yamabe H, Dodo Y, Kashii S, Nagata Y and Hiraoka M. Non-Hodgkin's lymphoma of the ocular adnexa. Acta Oncol 2001; 40: 485-490.
[20] Baldini L, Blini M, Guffanti A, Fossati V, Colombi M, La Targia ML, Bertoni F, Alietti A, Neri A and Bertoni G. Treatment and prognosis in a series of primary extranodal lymphomas of the ocular adnexa. Ann Oncol 1998; 9: 779-781.
[21] Stafford SL, Kozelsky TF, Garrity JA, Kurtin PJ, Leavitt JA, Martenson JA and Habermann TM. Orbital lymphoma: radiotherapy outcome and complications. Radiother Oncol 2001; 59: 139-144.
[22] Liao SL, Kao SC, Hou PK and Chen MS. Results of radiotherapy for orbital and adnexal lymphoma. Orbit 2002; 21: 117-123.
[23] Hasegawa M, Kojima M, Shioya M, Tamaki Y, Saitoh J, Sakurai H, Kitamoto Y, Suzuki Y, Niibe H and Nakano T. Treatment results of radiotherapy for malignant lymphoma of the orbit and histopathologic review according to the WHO classification. Int J Radiat Oncol Biol Phys 2003; 57: 172-176.
[24] Woolf DK, Ahmed M and Plowman PN. Primary lymphoma of the ocular adnexa (orbital lymphoma) and primary intraocular lymphoma. Clin Oncol (R Coll Radiol) 2012; 24: 339-344.
[25] Nam H, Ahn YC, Kim YD, Ko Y and Kim WS. Prognostic significance of anatomic subsites: results of radiation therapy for 66 patients with localized orbital marginal zone B cell lymphoma. Radiother Oncol 2009; 90: 236-241.
[26] Stefanovic A and Lossos IS. Extranodal marginal zone lymphoma of the ocular adnexa. Blood 2009; 114: 501-510.
[27] De Cicco L, Cella L, Liuzzi R, Solla R, Farella A, Punzo G, Tranfa F, Strianese D, Conson M, Bonavolonta G, Salvatore M and Pacelli R. Radiation therapy in primary orbital lymphoma: a single institution retrospective analysis. Radiat Oncol 2009; 4: 60.
[28] Ferrufino-Ponce ZK and Henderson BA. Radiotherapy and cataract formation. Semin Ophthalmol 2006; 21: 171-180.
[29] Decaudin D, Dendale R and Lumbroso-Le Rouic L. Treatment of mucosa-associated lymphoid tissue-type ocular adnexal lymphoma. Anticancer Drugs 2008; 19: 673-680.
[30] Aviles A, Neri N, Calva A, Huerta-Guzman J, Cleto S and Nambo MJ. Addition of a short course of chemotherapy did not improve outcome in patients with localized marginal B-cell lymphoma of the orbit. Oncology 2006; 70: 173-176.
[31] Tanimoto K, Kaneko A, Suzuki S, Sekiguchi N, Maruyama D, Kim SW, Watanabe T, Kobayashi Y, Kagami Y, Maeshima A, Matsuno Y and Tobinai K. Long-term follow-up results of no initial therapy for ocular adnexal MALT lymphoma. Ann Oncol 2006; 17: 135-140.
[32] Ferreri AJ, Guidoboni M, Ponzoni M, De Conciliis C, Dell'Oro S, Fleischhauer K, Caggiari L, Lettini AA, Dal Cin E, Ieri R, Freschi M, Villa E, Boiocchi M and Dolcetti R. Evidence for an association between chlamydia psittaci and ocular adnexal lymphomas. J Natl Cancer Inst 2004; 96: 586-594.
[33] Yoo C, Ryu MH, Huh J, Park JH, Kang HJ, Ahn HS, Lee Y, Kim MJ, Lee H, Kim TW, Chang HM, Lee JL and Kang YK. Chlamydia psittaci infection and clinicopathologic analysis of ocular adnexal lymphomas in Korea. Am J Hematol 2007; 82: 821-823.
[34] Vargas RL, Fallone E, Felgar RE, Friedberg JW, Arbini AA, Andersen AA and Rothberg PG. Is there an association between ocular adnexal lymphoma and infection with Chlamydia psittaci? The university of Rochester experience. Leuk Res 2006; 30: 547-551.
[35] Zhang GS, Winter JN, Variakojis D, Reich S, Lissner GS, Bryar P, Regner M, Mangold K and Kaul K. Lack of an association between chlamydia psittaci and ocular adnexal lymphoma. Leuk Lymphoma 2007; 48: 577-583.
[36] Mulder MM, Heddema ER, Pannekoek Y, Faridpooya K, Oud ME, Schilder-Tol E, Saeed P and Pals ST. No evidence for an association of ocular adnexal lymphoma with chlamydia psittaci in a cohort of patients from the Netherlands. Leuk Res 2006; 30: 1305-1307.
[37] Daibata M, Nemoto Y, Togitani K, Fukushima A, Ueno H, Ouchi K, Fukushi H, Imai S and Taguchi H. Absence of Chlamydia psittaci in ocular adnexal lymphoma from Japanese patients. Br J Haematol 2006; 132: 651-652.
[38] de Cremoux P, Subtil A, Ferreri AJ, Vincent-Salomon A, Ponzoni M, Chaoui D, Arnaud P, Lumbroso-Le Rouic L, Sacchetti F, Dendale R, Thioux M, Escande MC, Stern MH, Dolcetti R and Decaudin D. Re: evidence for an association between chlamydia psittaci and ocular adnexal lymphomas. J Natl Cancer Inst 2006; 98: 365-366.