• Clinical Research •

Clinical features and treatment outcomes of primary ocular adnexal mucosa-associated lymphoid tissue lymphoma: a single center retrospective analysis of 64 patients in China

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Abstract

• AIM: To investigate the clinical features, treatment and prognosis of primary ocular adnexal mucosa-associated lymphoid tissue lymphoma (POAML).

• METHODS: A retrospective analysis was performed on 64 patients with POAML who were admitted to the First Affiliated Hospital of Zhengzhou University from January 2006 to December 2018.

• RESULTS: With a median follow-up of 61mo (range, 2-156mo), estimated overall survival (OS) rate and progression-free survival (PFS) rate at 10y reached 94.5% and 61.5%, respectively. Median OS time and PFS time were not reached. During this period, only 3 patients died, but none of them died directly due to disease progression. One patient (1.6%) developed transformation to diffuse large B-cell lymphoma (DLBCL). Of the 56 patients achieved complete remission after first-line treatment, 5 (8.9%) developed local and/or systemic relapse eventually. Patients ≥60y had significantly shorter PFS than younger patients (*P*=0.01). For patients with early stages (Ann Arbor stage I and stage II), univariate analysis confirmed that radiotherapy dose lower than 32 Gy were independently associated with shorter PFS (*P*=0.04). Other factors including gender, bone marrow involvement, the initial location of the disease, and the laterality were not associated with PFS.

• CONCLUSION: The data from our center indicate that POAML has a slow clinical progression and has an excellent clinical outcome. Patients with POAML harbor a continual risk of relaps and transformation to aggressive subtype of lymphoma.

• KEYWORDS: primary ocular adnexal MALT lymphoma; mucosa-associated lymphoid tissue; involved site radiation therapy; immunochemotherapy

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INTRODUCTION

Primary ocular adnexal lymphoma (POAL) is extranodal lymphoma that often occurs in the orbit, lacrimal gland, conjunctiva, and eyelids, accounting for up to 55% of all ocular adnexal tumors[1-2]. In the 1970s, the annual incidence of POAL was about 0.28 per 100 000, which showed a gradual increase in the past 40y[3-4]. Most of the POAL belong to non-Hodgkin's lymphoma (NHL), and the most common pathological subtype is extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) which accounts for 35% to 88% of POAL cases[5-7].

Despite significant advances in studies of etiology, clinical manifestations and treatment of primary ocular adnexal mucosa-associated lymphoid tissue lymphoma (POAML) in decades, there are still many important etiological and prognostic issues that remain unresolved[8-10]. Although some studies have reported the close relationship between Chlamydia psittaci and POAML in certain geographic areas, this connection is not universal and there may be other inducing

conditions[11]. In terms of treatment, 85%-100% of patients with limited stages can get lasting clinical remission by receiving radiotherapy treatment (RT), but the optimal dose of RT remains controversial[12]. In addition, although radiotherapy can perform good local control, it has been reported that 5%-32% of patients will have systemic recurrence[8,13-14]. Regarding the use of immunochemotherapy alone or combined with other treatment modalities, overall data is limited due to the insufficient number of patients and lack of large prospective multicenter studies, there is no consensus on the initial treatment guidelines for patients with POAML. The clinical features of the initial disease site, patient age, stage or initial performance are still controversial for the prognosis of patients with POAML.

Currently, there are very few large cohort studies reported on POAML in China. Consequently, we conducted a single-institute retrospective analysis of 64 patients with POAML received treatment at our institution between 2006 and 2018. The purpose of this analysis was to analyze the impact of initial clinical presentation, staging and different treatment modalities on prognosis, and will provide useful guidelines for POAML treatment.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the Ethical Review Committee of the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China. All procedures adhered to the tenets of the Declaration of Helsinki for research involving human subjects. Written informed consents were obtained from all participants enrolled in this study.

Subjects and Enrollment Criteria This study included 64 patients with POAML who were admitted to the First Affiliated Hospital of Zhengzhou University from January 2006 to December 2018. Patients enrolled in this study were required to have biopsy material that diagnosed MALT lymphoma, according to 2016 World Health Organization (WHO) classification criteria for lymphoid hematopoietic tumors.

Information about the patients' gender, age, Eastern Cooperative Oncology Group (ECOG) physical status (PS) score, the symptoms and signs present at the initial diagnosis, imaging data, treatment plan and prognosis were collected and recorded in detail. All patients received comprehensive laboratory examinations, including blood routine test, liver and kidney function, lactate dehydrogenase (LDH), β2-microglobulin, serum Immunofixation electrophoresis, coagulation function and hepatitis B virus-DNA quantification. Bone marrow smears and biopsies were also performed.

Staging was based on the Ann Arbor standard. Prognosis stratification was performed according to MALT lymphoma international prognostic index (MALT-IPI). Age ≥70y, Ann Arbor stage III or IV and serum LDH level above normal are prognostic disadvantages. One point was calculated for each unfavorable factor. Patients with a total score of 0 were identified as low-risk, with score of 1 were classified as intermediate risk, ≥2 were divided into high-risk patients.

Treatment Patients' treatment plans were determined mainly based on the stage of the disease and judgments of physician. Treatment methods are diversity including local therapy (surgery alone, radiotherapy alone, surgery combined with radiotherapy) and systemic therapy (immunochemotherapy, surgery combined with radiotherapy and immunotherapy, radiotherapy and immunochemotherapy). Patients with limited stages were most commonly treated with local therapy, mainly radiotherapy.

Statistical Analysis Overall survival (OS) is the length time from the initial disease diagnosis to death from any cause or the last follow-up. Progression-free survival (PFS) was defined as the time from diagnosis to disease recurrence, pathological transformation, relapse, or death. Efficacy assessment referred to the Lugano mitigation criteria for NHL, which includes complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The sum of the CR rate and the PR rate is the objective response rate (ORR). No patients were excluded from efficacy and survival analysis because of missing efficacy information. Statistical analysis was performed using SPSS 17.0 software (SPSS, Chicago, IL, USA), survival curve was drawn by Kaplan-Meier method, and single factor survival analysis was performed by Log-rank test. $P \leq 0.05$ was considered statistically significant.

RESULTS

Clinical Characteristics Between 2006 and 2018, 64 patients with POAML received treatment at our institutions. Median age at diagnosis was 58y (range, 41-82y), including 36 males (56.3%) and 28 females (43.7%). The remaining clinical features are detailed in Table 1.

Relevant previous medical history was Sjögren's Syndrome (SS) and eye disorders in 2 patients (3.1%) and 7 patients (10.9%), respectively. Chronic hepatitis B infections were detected in 2 (3.1%) patients. Only 51 patients underwent the monoclonal gammopathy test through blood examination, of which 5 patients were immunoglobulin M (IgM) type, 1 patient IgG type, and 1 patient IgA type.

Orbit were the most common primary site involved (39 patients, 60.9%), followed by conjunctiva (15 patients, 23.4%), lacrimal glands (11 patients, 17.2%) and eyelids (12 patients, 18.8%). Among them, 5 cases were bilateral lesions (7.8%). The clinical characteristics of POAML are diverse according to the location of tumors. Common symptoms of patients in this study included eyelid swelling, proptosis, conjunctival injection, painless palpable mass, ptosis, foreign body sensation, blurred vision, and blurred vision.

Table 1 Clinical features of the 64 patients with primary ocular adnexal MALT lymphoma

Characteristic	*n* (%)
Gender	
Male	36 (56.3)
Female	28 (43.7)
Anatomical location	
Orbit	39 (60.9)
Conjunctiva	15 (23.4)
Lacrimal gland	11 (17.2)
Eyelids	12 (18.8)
Bilateral disease	5 (7.8)
Ann Arbor stage	
I	52 (81.3)
II	3 (4.7)
III	4 (6.3)
IV	5 (7.8)
MALT-IPI score	
0	48 (75.0)
1	10 (15.6)
≥2	6 (9.4)
ECOG PS score	
0	61 (95.3)
≥1	3 (4.7)
LDH above normal	6 (9.4)
Bone marrow involvement	4 (6.3)

MALT-IPI: Mucosa-associated lymphoid tissue international prognostic index; LDH: Lactate dehydrogenase; ECOG PS score: Eastern Cooperative Oncology Group physical status score.

All the patients underwent whole-body imaging or bone marrow examination. At the time of presentation, 52 (81.3%) patients and 3 (4.7%) patients were with limited stage, Ann Arbor stage I, II, respectively. 4 (6.3%) patients and 5 (7.8%) patients were with stage III and stage IV, respectively. The majority of patients had good physical condition with an ECOG PS score of 0 (95.3%, 61/64). Risk stratification showed that most patients were at low and medium risk (58 patients, 90.6%), only 6 patients (9.4%) were evaluated as high risk with MALT-IPI score ≥2. Among them, 6 patients (9.4%) were detected with increased LDH at the time of initial diagnosis.

Treatment, Response, and Follow-up A total of 64 patients had available data of first-line therapy, response and outcome. Details of response rates and relapses rates of varied treatment modalities are summarized in Table 2.

Among the patients with limited stage (Ann Arbor stage I and stage II), there were 30 patients received involved site radiation therapy (ISRT) alone, and 4 patients only received surgery treatment. Fifteen patients and 4 patients underwent the ISRT combined with surgery and ISRT combined with rituximab, respectively. Only 3 (5.5%) of these patients with limited stages did not achieve CR. With a median follow up of 58.5mo (range, 2-156), the incidence of relapse in the local treatment groups (ISRT and/or surgery) was not significantly different than the patients received systemic treatment (*P*-value is 0.92).

Table 2 Outcomes according to treatment modalities and disease stage at presentation

Ann Arbor stage	*n*	CR	Relapse
I, II			
Local treatment			
ISRT	30	27	5
Surgery only	4	4	2
Surgery+ISRT	15	13	2
Systemic treatment			
Rituximab+ISRT	4	4	1
Surgery+rituximab+ISRT	2	2	0
III, IV			
R-CVP	5	3	2
R-CHOP	3	2	1
R-CVP+ISRT	1	1	0

ISRT: Involved site radiation therapy; R-CVP: Rituximab, cyclophosphamide, vincristine/vindesine, prednisone; R-CHOP: Rituximab, cyclophosphamide, epirubicin, vincristine/vindesine, prednisone; CR: Complete response.

Among the patients with advanced stage (Ann Arbor stage III and stage IV), five patients of them were treated with rituximab, cyclophosphamide, vincristine/vindesine, prednisone (R-CVP) regimen, and 3 patients were received rituximab, cyclophosphamide, epirubicin, vincristine/vindesine, prednisone (R-CHOP). Only 1 patient was treated with R-CVP combined with ISRT, since after the systemic therapy, the eyelid involved did not reach CR, and local ISRT was followed as the adjuvant treatment. Although 3 (33.3%) of these patients with advanced stages did not reach CR after the initial treatment, the incidence of relapse of the patients with advanced stage was no significant difference with the patients with the limited stages groups (*P*-value is 0.29). Overall, the dose of radiotherapy varied though our study period, ranging from 26 to 45 Gy (median dose, 32 Gy). First-line treatment resulted in CR in 56 patients (87.5%) and PR in 4 patients (6.3%; 1 patient with stage I, 1 patient with stage IV), SD in 2 patients with stage II, and PD in 3 patients (1 patient with stage I, 1 patient with stage II, and 1 patient with stage III).

Survival, Outcome and Prognostic Factors Follow-up data were available for all patients with a median follow-up of 61mo, with ranging from 2 to 156mo. During this period of time, only 3 patients died, but none of them died directly of disease progression. The OS rate is 94.5% at 10y (Figure 1A). One patient (1.6%) developed transformation to diffuse large

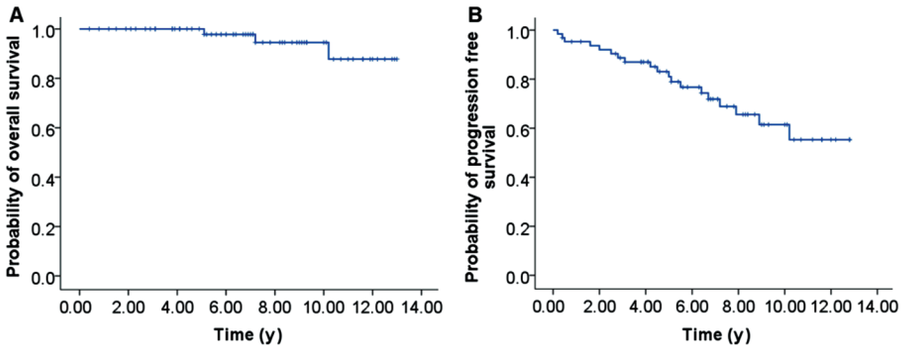

Figure 1 Survival of patients with POAML A: OS; B: PFS.

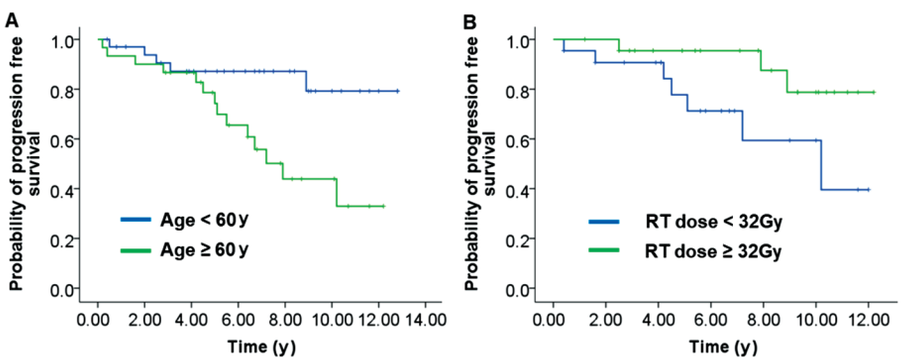

Figure 2 Univariate analysis of factors associated with PFS A: According to the age of all patients: aged <60y versus ≥60y; B: According to the radiotherapy dose in patients with stage I and II: RT dose <32 Gy versus ≥32 Gy.

B-cell lymphoma (DLBCL). Of the 56 patients achieved CR after initial treatment, 5 patients (8.9%) eventually had local and/or systemic relapse. Two patients who underwent surgery alone in the stage I were progressed at 19 and 75mo. Three patients who underwent ISRT alone in the limited stages were progressed at 34, 37 and 51mo. The PFS estimated by Kaplan-Meier analyses at 1, 5, and 10y were 93.7%, 81.0%, and 61.5%, respectively (Figure 1B). The median OS time and PFS time were not reached.

Associations between age, gender, stage, LDH levels, bone marrow involvement, treatment, and outcome were examined. Since there is no disease progression-related death, we focused on analyzing the factors related with PFS. Among these factors, gender, bone marrow involvement, the initial location of the disease, and the laterality were not associated with PFS. The identified prognostic factors including age and radiotherapy dose are shown in Figure 2. Patients ≥60y had significantly shorter PFS than younger patients (P=0.01; Figure 2A). For patients with stage I and stage II, univariate analysis confirmed that radiotherapy dose lower than 32 Gy were associated with shorter independently (P=0.04; Figure 2B).

DISCUSSION

Lymphoma is the most common type of adult primary ocular adnexal tumors, and POAL mainly involves the orbit, conjunctiva, eyelids, lacrimal glands, and lacrimal sac. Among the pathological types, the incidence of MALT lymphoma was the highest, accounting for 62%, and its prognosis was significantly better than other pathological types. Follicular lymphoma (17%) is the second most common subtype followed by DLBCL (10%)[15]. The present study summarized 64 cases of POAML in our single institute, which, to our best knowledge, is a largest retrospective study on POAML in China. Our findings are not only consistent with some results of the previously reported observations, but also provided new information on prognostic factors, treatment and outcomes specifically for Chinese patients. Multiple retrospective studies from western countries have reported clinical features of POAML, including female preponderance, median age about 65y, and frequent occurrence in the orbit[8]. However, studies from other Asian counties described a significantly younger median age about 45y and a male prevalence[5,9,16]. Median age at diagnosis of our cohort is 58 years old, and the ratio of male to female is 1.3:1, which is similar to that reported in Asian countries such as Japan and South Korea. These results suggest that there is a significant difference between Asian countries and western countries in the age and gender composition of POAML.

The literature reports that ocular adnexal lymphoma most often affects orbital, bilateral involvement of about 7% to 24%, bone marrow involvement of about 2% to 8.6%[8,17-19], our data is consistent with previous reports with orbit involvement (60.9%), bilateral disease (7.8%), and bone

marrow involvement (6.3%). Although researchers from Miller School of Medicine demonstrated that bilateral involvement was independently associated with inferior outcome with statistically shorter OS and PFS than in patients with unilateral disease[8]. Data from our center was exhibited no statistical connection between bilateral disease and the outcome.

Majority of the patients were with limited stages at the time of initial diagnosis. The patients with stage I accounted for 52 cases (81.3%), with low and intermediate risk. Only 1 patient had B symptoms (unexplained fever >38℃), and low proportion of elevated LDH levels were detected (6 patients, 9.4%). These clinical manifestations match the indolent clinical course with POAML. Desai *et al*[8] reported that there was no significant correlation between bone marrow involvement and patient prognosis, and it was suggested that bone marrow biopsy may not be necessary for the staging of POAML patients. In our study, 4 patients were accompanied by bone marrow involvement in addition to ocular localized lesions. After treatment, PR and above were alleviated. There was also no significant difference in PFS for patients whether had the bone marrow involvement (P=0.483).

The commonly recognized pathogenesis of POAML include chronic inflammation (for example, C psittaci) or autoimmune disorders that produce sustained antigenic stimulation, resulting in localized lymphoid tissue hyperplasia. Sustained chronic antigen stimulation can cause genetic instability, leading to the proliferation of normal lymphoid cell malignant clones, which eventually transform into MALT lymphoma. The C psittaci tests were negative in all patients in our study. However, reports from other geographic showed that C psittaci infection was found to be closely related to the occurrence of the disease[11,14]. Compared with normal population controls, patients with autoimmune disorders, such as rheumatoid arthritis, SS and systemic lupus erythematosus, are more likely to develop MALT lymphoma, which again suggests an important role for autoimmune disorders in the pathogenesis of POAML[20]. Two patients in our study had a history SS and received treatment. Engels *et al*[21] reported that patients with SS had a 1000-fold increased risk of developing MALT-type lymphoma.

Treatment of POAML is effective by surgical resection, radiotherapy and chemotherapy. ISRT performed an excellent local control (86% to 100%) of POAML patients at Ann Arbor stage I in all previous studies. Consistent with previous reports, ISRT also performed local control in 87% of our patients at stage I. Although the excellent initial remission to ISRT in stage I patients, a continuous risk of local or distant relapse or progression of 6.7% at 1y, 10% at 5y, and 16.7% at 10y were observed. Desai *et al*[8] showed that local and systemic relapses or progression of 5.1% at 1y, 17.5% at 5y, and 31% at 10y for the patients with Ann Arbor stage I after radiotherapy as initial treatment. Decaudin *et al*[22] summarized that systemic relapses (6% to 50%) and local relapses (up to 15%) were observed in patients treated with radiotherapy in a POAML review. Transformation to aggressive lymphoma and central nervous system involvement has also been reported. The cause of recurrence may be explained by microscopic disease remaining outside the surgical or radiotherapy treatment area. Therefore, although the patient can achieve good local control, some patients will still have distant recurrence in a short time or years. Kim *et al*[23] reported that patients with POAML have high risk factors, surgery combined with immunochemotherapy may reduce the recurrence rate. Six patients with stage I-II POAML in our center underwent immunotherapy or immunochemotherapy after local treatment, and all of them reached CR after initial treatment. Only one patient developed disease progression as of the end of follow-up. Although we found that patients with high MALT-IPI scores, immunotherapy or immunochemotherapy combined with local radiotherapy, have the tendency to improve PFS compared with ISRT alone. However, the reason may be the limited number of cases, and there is no statistical difference in PFS between these two modalities.

The optimal dose of radiotherapy has not yet reached a consensus, high dose of radiotherapy can reduce the recurrence rate, but the incidence of adverse reactions related to radiotherapy is correspondingly increased. Desai *et al*[8], who analyzed 98 patients with stage I, demonstrated that whether the dose of RT (<30.6 Gy *vs* ≥30.6 Gy, P=0.0001) or doses of (<36 Gy *vs* ≥36 Gy, P=0.0007) were related with PFS, but not OS. Fung *et al*[24] reported a similar observation that 5-year local control rate was 81% in patients treated with RT at doses of <30 Gy, but in those received RT dose ≥30 Gy5-year local control rate reached 100% (P<0.01). The optimal radiation dose 30.6-32.4 Gy in 1.8 Gy fractions was suggested for POAML patients. The dose of radiotherapy varied though our study period, ranging from 26 to 45 Gy (median dose, 32 Gy). We demonstrated that RT at dose lower than 32 Gy led to higher incidence of local and systemic recurrence and shorter PFS compared with patients received RT dose ≥32 Gy. Therefore, the range of RT effective doses reported in the literature is very broad. Overall, the analysis showed that higher RT doses led to better PFS, but also increased the risk of local acute and chronic complications. To demonstrate whether lower dose of radiotherapy combined with immunotherapy has superior PFS than the radiotherapy alone, long-term follow-up and large cohort study are required.

In summary, our study confirms that POAML is relatively indolent disease, characterized by long survival, the persistent risk of recurrence and transformation to aggressive lymphoma.

Through partial results reported in this article is not completely consistent with previous reports, and there is controversy. We demonstrated that age and radiotherapy dose affected the outcome of POAML patients. There findings will be helpful in stratification of POAML patients in future treatment studies. Prospective clinical studies, multi-center collaboration, and large sample statistics may help us understand the disease more deeply.

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