Characteristics and treatment outcomes of patients with primary ocular adnexal lymphoma in Northern Thailand

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Abstract

Purpose: To assess the characteristics and treatment outcomes of patients with primary ocular adnexal lymphoma (OAL) in Northern Thailand.

Design: Retrospective cohort study.

Methods: Data was collected from electronic medical records and operative notes from Chiang Mai University Hospital between January 2009 and December 2014. All available tissue biopsies of 54 patients were reviewed by agreement of two pathologists. The clinical characteristics and treatment outcomes were collected and analyzed.

Results: A total number of 54 patients were identified of which 57.4% were female. The median age was 61.0 years (range, 4-86). The most common subtype of lymphoma was extranodal marginal zone lymphoma (ENMZL) of mucosa-associated lymphoid tissue (MALT) (n = 46, 85.2%). Seventy-five percent of the patients presented with a mass at the ocular adnexa, while 14.8% of the patients presented with proptosis. The sites of origin were as follows: lacrimal (46.3%), orbit (31.5%), conjunctiva (13%) and eyelid (7.4%). Two-thirds of the patients had Ann-Arbor Stage I, while 22% of patients had Stage IV. The majority of the patients (68.1%) had a low-risk international prognosis index (IPI). Treatment modalities involved field radiation (IFRT, 50%), chemotherapy (31.6%), combined chemoradiotherapy (7.9%) and surgical resection (10.5%). The overall response rate was 100% with a complete response rate of 77.8%. In patients with low-grade lymphoma, including MALT lymphoma, the 3-year progression-free survival (PFS) and overall survival were 69.9% and 92.5%, respectively.

Conclusion: ENMZL of MALT was the major subtype of primary OAL. Radiotherapy was an effective treatment for the lower stages of disease providing a high response rate and encouraging survival outcomes.

Keywords: extranodal marginal zone lymphoma of mucosal-associated lymphoid tissue, ocular adnexal lymphoma, radiotherapy, treatment modalities

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Introduction
Primary ocular adnexal lymphoma (OAL) is the most common malignancy of the eye. Primary OAL is defined as lymphoma that occurs at the conjunctiva, lacrimal apparatus, eyelid and in the orbit. OAL comprised 2% of non-Hodgkin lymphoma and 8% of extranodal lymphoma. The most common subtype is extranodal marginal zone lymphoma (ENMZL) of mucosa-associated lymphoid tissue (MALT), which usually originates from B cells. The most frequent site of origin is the orbit 40%, conjunctiva 35% to 40%, lacrimal apparatus 10% to 15% and eyelid 10%. The average age for diagnosis is from 50 to 70 years. Bilateral disease will be seen in 10% to 15%.

Most of the patients (85-90%) were diagnosed with Ann-Arbor Stage I which responded very well to radiotherapy. A complete response rate was 85% to 90%, and only 10% to 15% of the patients had Ann-Arbor Stage IV. Currently, there are no standard treatment guidelines specifically for OAL. Patients were treated as ENMZL lymphoma in the other sites. Patients with Stage I disease were commonly treated with involved field radiotherapy.

The majority of previous reports were from Western countries. In Thailand, there were few publications regarding primary OAL. To improve the diagnosis and quality of treatment in a patient with OAL, we conducted a retrospective review to study the characteristics and treatment outcomes of OAL patients in Northern Thailand.

Material and methods
This study was approved by the Institutional Review Board of Chiang Mai University Hospital, Chiang Mai, Thailand. The medical records and operative notes between January 2009 and December 2014 were reviewed to recruit patients with OAL. The inclusion criteria of patients in this study were patients diagnosed with OAL between January 2009 and December 2014 who had been followed for at least 1 year. The patients with follow-up of less than 1 year were excluded from the study. All available tissue biopsies of these patients were reviewed by two pathologists according to the 2008 World Health Organization guidelines. Immunohistochemical study routine was done to identify the subtype of lymphoma which included CD3, CD5, CD10 and CD20; however, because of the limitation of resource and available tissues, we cannot perform genetic study, but both of the experienced pathologists had a consensus agreement with the diagnosis with available tissues.

Data were collected including age at diagnosis, gender, underlying disease, clinical presentation, time to diagnosis, procedure of tissue biopsy, anatomical location, laterality, subtype of OAL, immunophenotype, Ann-Arbor staging, number of extranodal sites and performance status (ECOG). Additional data included serum
lactic dehydrogenase (LDH) level, anti-HIV, hepatitis B and C status, international prognostic index (IPI) and treatment modalities including type of chemotherapy, radiotherapy, response to treatment, recurrent status of disease, salvage therapy and current status of the patients. All treatment outcomes were evaluated for at least 1 year and disease activity was evaluated at the last time of follow-up.

**Statistical analysis**
The demographic and response rates were analyzed with descriptive statistics. Overall survival (OS) was measured from the date of diagnosis to the date of last follow-up or death from any cause. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of last follow-up, second relapse/progression or death from any cause. Probabilities of OS and second PFS were estimated by using the Kaplan–Meier method and using log-rank test for survival comparison. All statistical analyses were performed using SPSS 16.0 for Windows (SPSS, Chicago, IL).

**Results**

**Patients**
Fifty-four patients were identified with primary OAL between January 2009 and December 2014. Demographic and clinical characteristics of primary OAL are summarized in Table 1. There were 31 females (57.4%) with a median age of 61 years (range, 4-86 years). The most common subtype of lymphoma was ENMZL of MALT (n = 46, 85.2%). Other histologic subtypes included diffuse large B-cell lymphoma (DLBCL, n = 3, 5.6%), peripheral T-cell lymphoma (PTCL, n = 3, 5.6%), MALT lymphoma with large cell transformation (n = 1) and small lymphocytic lymphoma (SLL, n = 1).

A palpable mass was the main presenting symptom (75.9%). Other manifestations were proptosis (14.8%), cellulitis (5.6%) and eye pain (3.7%). The median interval between onset of the first symptoms and the date of diagnosis was five months (range, 0.5-84 months). Anatomically the tumors were distributed as follows: lacrimal (46.3%), orbit (31.5%), conjunctiva (13%) and eyelid (7.4%). Most of the patients present with unilateral (75.9%). The primary immunophenotype was B-cell origin (94.4%).

At presentation, 32 (59.3%) patients had Ann-Arbor Stage I, six (12%) patients had Ann-Arbor Stage II, one patient had Ann-Arbor Stage III and 11 (22%) patients had Ann-Arbor Stage IV. Fifty-two patients (96.3%) had ECOG 0; therefore, the majority of patients with OAL were fully active and able to carry on all pre-disease activities without restriction.

Only two (4.8%) patients were previously diagnosed with HIV before presenting with primary OAL. The majority of the patients had a normal serum LDH level (94%) and lower-risk IPI (80.9%). There were few patients with HBV (n = 1) and HCV (n = 1) infection.
| Characteristics                          | Number of patients (%) |
|-----------------------------------------|------------------------|
| Median age of diagnosis                 | 61.0 years (range, 4-86) |
| Female                                  | 31 (57.4%)             |
| Clinical presentation                   |                        |
| • Palpable mass                         | 41 (75.9%)             |
| • Proptosis                             | 8 (14.8%)              |
| • Cellulitis                            | 3 (5.6%)               |
| • Eye pain                              | 2 (3.7%)               |
| Median time to diagnosis                | 5.0 months (range, 0.5-84) |
| Anatomical location                     |                        |
| Lacrimal                                | 25 (46.3%)             |
| Orbit                                   | 17 (31.5%)             |
| Conjunctiva                             | 7 (13%)                |
| Eyelid                                  | 4 (7.4%)               |
| Lacrimal and conjunctiva                | 1 (1.9%)               |
| Laterality: Unilateral                  | 41 (75.9%)             |
| Subtype of lymphoma                     |                        |
| • MALT lymphoma                         | 46 (85.2%)             |
| • DLBCL                                 | 3 (5.6%)               |
| • PTCL                                  | 3 (5.6%)               |
| • MALT lymphoma with large cell transformation | 1 (1.9%)               |
| • SLL                                   | 1 (1.9%)               |
| Immunophenotype: B-cell origin          | 51 (94.4%)             |
| Ann-Arbor staging                       |                        |
| • I                                     | 32 (64%)               |
| • II                                    | 6 (12%)                |
| • III                                   | 1 (2%)                 |
| • IV                                    | 11 (22%)               |
| Performance status (ECOG)               |                        |
| • 0                                     | 52 (96.3%)             |
| • 1                                     | 2 (3.7%)               |
| IPI                                     |                        |
| • Low risk                              | 32 (68.1%)             |
| • Low-intermediate risk                 | 6 (12.8%)              |
| • High-intermediate risk                | 7 (14.9%)              |
| • High risk                             | 2 (4.3%)               |
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| Characteristics                  | Number of patients (%) |
|----------------------------------|------------------------|
| LDH level: normal (<246)/high    | 45 (93.8%)/3 (6.2%)    |
| HIV status: positive             | 2 (4.8%)               |
| HBV infection: positive          | 1 (2.4%)               |
| HCV infection: positive          | 1 (2.4%)               |

**Treatment and outcomes**

Treatment modalities were as follows: IFRT (50%), chemotherapy (31.6%), combined chemoradiotherapy (7.9%) and surgical resection (10.5%). The most common regimen for chemotherapy was CHOP which was comprised of cyclophosphamide, doxorubicin, vincristine and prednisolone (40%). The other regimens were CP (chlorambucil and prednisolone, 26.7%), CVP (cyclophosphamide, vincristine and prednisolone, 20%), and ALL protocol (n = 1) (Table 2).

Treatment outcomes were categorized according to the subtype and staging of lymphoma (Table 3). Indolent lymphoma included ENMZL of MALT and SLL, while aggressive lymphoma comprised of DLBCL, PTCL and MALT lymphoma with large cell transformation. The response rate after treatment in patients either with indolent and aggressive lymphoma was 100%. Eleven (20.4%) patients in this study had disease progression or relapse. The 3-year PFS and OS of patients with indolent lymphoma were 69.9 and 92.5%, respectively, which appeared to be better than of those with aggressive lymphoma (3-year PFS and OS of 42.9% [p = 0.12] and 42.9% [p < 0.0001]) (Fig. 1A and B).

**Table 2. Treatment modalities**

| Treatment modalities       | Watch and wait (n = 16) | Treatment (n = 38) |
|----------------------------|-------------------------|--------------------|
| Radiotherapy               |                         | 19 (50%)           |
| **Chemotherapy**           |                         |                    |
| CHOP                       |                         | 12 (31.6%)         |
| CVP                        |                         | 5                  |
| CP                         |                         | 3                  |
| ALL protocol               |                         | 3                  |
| Surgery                    |                         | 1                  |
| Chemotherapy and radiotherapy |                 | 4 (7.9%)           |
|                            |                         | 3 (10.5%)          |
Table 3. Treatment outcomes categorized according to subtype and staging of lymphoma

| Type of lymphoma  | Staging | N   | OR (%) (CR, %) | 3-year PFS (%) | 3-year OS (%) |
|-------------------|---------|-----|----------------|----------------|---------------|
| Indolent lymphoma | I-II    | 26  | 100 (76.9)     | 70.2           | 69.9          |
|                   | III-IV  | 5   | 100 (60)       | 55.6           | 50.0          |
| Aggressive lymphoma | I-II | 3   | 100 (100)     | 33.3           | 42.9          |
|                   | III-IV  | 2   | 100 (100)     | 66.7           | 66.7          |

Fig. 1. (A) Kaplan–Meier PFS according to clinical subtypes of symptoms. (B) Kaplan–Meier OS according to clinical subtypes of lymphoma.
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For patient with limited stage indolent lymphoma, either unilateral or bilateral ocular adnexal involvement had no significant effect on event-free survival (EFS) and OS, although patient with unilateral involvement had a trend of better EFS (median EFS was not reached) than those with bilateral involvement (EFS = 29 months, p = 0.025). Moreover, in this particular group patients, anatomical involvement had no effect on both EFS and OS (p = 0.66).

Among patients with indolent lymphoma, those with lower stages of disease had a superior 3-year PFS (70.2%) and 3-year OS (96.8%) than those with advanced stage disease with 3-year PFS and OS of 55.6% and 50%, respectively.

Discussion

Over the past decade, patients suspected to have primary OAL were transferred to Chiang Mai University Hospital, which is a tertiary care hospital in Northern Thailand. A multidisciplinary team was composed of an ophthalmologist, haematologist, pathologist and radiotherapists. With limited information on the patient treatment modalities and outcomes, it was difficult to explain to the patients regarding their disease status and prognosis. This study will provide a better understanding of patient characteristics and long-term outcomes after therapy.

The most common subtype of OAL in this study was ENMZL of MALT. Interestingly in our study, there was a higher proportion of patient of MALT lymphoma (85.2%) when compared with previous reports from the Asian and Western countries in which MALT lymphoma shows 30% to 70% of OAL11–16 (Table 4). A palpable mass was the most common manifestation with a wide range of times from the first sign of symptoms to diagnosis of 0.5 to 84 months. This may be explained by the non-painful and slow progress of the disease. OAL commonly occurred in elderly patients which correlated with previous studies.11–15,17–19

Meunier et al.,12 found that elevated LDH in low-grade lymphoma patients negatively predicted disease-free survival; however, in this series, most of the patients (93.8%) had a normal volume of LDH. Ferreri et al.20,21 demonstrated an association between Chlamydia psittaci and OAL, but in our study, we have a limited number of tissues and methods to detect C. psittaci; therefore we did not find this association.

The most common site of origin was the lacrimal gland, which was different from previous studies,12,14,16,17–19 but correlated with a previous study in Thailand.10 Most of the patients had Ann-Arbor Stage I and radiotherapy was the first-line treatment option which concurred with previous reports.12,14,15,17–19 Rituximab, anti-CD20 antibody, has been reported to have a good activity on OAL.22–28 Due to its high cost, there was only one patient in this cohort who received rituximab with complete response after treatment.
In this study, an indolent subtype of primary OAL had an excellent outcome with a 3-year PFS and OS of 69.9% and 92.5%, respectively. Of these patients with indolent lymphoma, those with a limited stage had superior survival than those with advanced stage disease. Lymphoma is a chemo- and radio-sensitive disease; therefore, both aggressive and indolent lymphoma showed a good response rate after treatment. However, aggressive lymphoma nature had a high chance of progression and relapse disease afterward. Many studies from Western and Asian countries also showed similar outcomes with high PFS and OS after radiotherapy.\textsuperscript{11,12,14,15,18,19}

This study had several limitations. First, it was retrospective in nature; therefore, there was a limitation in data collection. Second, ocular adnexa was not a common site of aggressive lymphoma, so we were not able to find a predicting prognosis factor in this subgroup of lymphoma. In the future, we should find a prognosis factor and association with \textit{C. psittaci} in a larger study and focus on ENMZL of MALT which are the most common subtypes. The appropriate dosage of radiation and complications should also be further explored.

In conclusion, in Northern Thailand, ENMZL of MALT was the most common subtype of primary OAL. In a limited stage of disease, initial treatment with radiotherapy provided excellent outcomes.
## Table 4. Characteristics and treatment outcomes of patients with OAL

| Study          | Country of study | N   | Subtype of lymphoma, % | Clinical presentation, % | Treatment modality, % | PFS, DFS, % | OS, % |
|----------------|------------------|-----|------------------------|--------------------------|-----------------------|-------------|-------|
| This study     | Thailand         | 54  | MALT, 85.2% DLBCL, 5.6% | Palpable mass, 75.9% | RT, 50% CT, 31.6%     | EFS-3-LG, 69.9% | OS-3-LG, 92.5% |
| Jenkins et al. | Great Britain    | 192 | MALT, 43% LPL, 23% FCL, 14% | NA | NA | EFS-5-LG, 88% EFS-5-HG, 52% | NA |
| Coupland et al. | Germany          | 136 | All MALT                | NA | NA | NA | NA |
| Meunier et al. | France           | 145 | MALT, 36% LPL, 22% LL, 10% | Conjunctival lesion, 32% Exophthalmos, 27% Palpable mass, 19% | RT, 42% RT+CT, 25% | EFS-5-LG, 68% EFS-5-HG, 43% | NA |
| Ferry et al.   | USA              | 353 | MALT, 52% FCL, 23% DLBCL, 8% | Palpable mass, 69% | RT, 50% CT, 25% | NA | NA |

(continued)
| Study           | Country of study | N  | Subtype of lymphoma, % | Clinical presentation, % | Anatomical location, % | Treatment modality, % | PFS, EFS, DFS, % | OS, %          |
|-----------------|------------------|----|------------------------|--------------------------|------------------------|-----------------------|-----------------|----------------|
| Tanimoto et al. | Japan            | 114| All MALT               | NA                      | Orbit, 59% Conjunctiva, 36% | RT, 51%               | EFS-5, 96% EFS-10, 57% EFS-15, 39% | OS-5, 96% OS-10, 92% OS-15, 71% |
| Bayraktar et al. | Great Britain    | 90 | All MALT               | Conjunctival, visible lesion Orbital and lacrimal, periorbital edema | Orbit, 46% Conjunctiva, 36% | RT, 85%               | EFS-5, 73.6% EFS-10, 52.6% | NA             |
| Portell et al.  | USA              | 95 | MALT, 70.2% FCL, 14.9% DLBCL, 3.2% | NA                      | Orbit, 58.9% Conjunctiva, 41.1% Uvea, 18.9% | RT, 56% CT, 12%       | NA              | OS-5, 74.2%    |
| Sniegowski et al.| USA              | 82 | MALT, 65.9% FCL, 14.6% DLBCL, 14.6% | NA                      | NA                     | RT, 34.1% CT, 32.9%   | DFS-5, 55.9% | OS-5, 85.8%    |

N, number of cases; NA, not applicable
Lymphoma type: DLBCL, diffuse large B-cell lymphoma; FCL, follicle centre lymphoma; LL, lymphocytic lymphoma; LPL, lymphoplasmacytoid/lymphoplasmacytic lymphoma; MALT, mucosal-associated lymphoid tissue; PTCL, peripheral T-cell lymphoma
Treatment modalities: CT, chemotherapy; RT, radiotherapy
DFS-N, N-year disease-free survival; EFS-N, N-year event-free survival; PFS-N, N-year progression-free survival
HG, high-grade lymphoma, LG, low-grade lymphoma
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