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Primary Pulmonary Non-Hodgkin's Lymphoma

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Background: Primary pulmonary non-Hodgkin's lymphoma is a very rare neoplasm. It is represented most commonly by marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type. Although there have been a few reviews of this lymphoma, clinical features, diagnostic procedure, optimal management and prognostic factors have not been well defined.
Methods: We reviewed the medical records of 24 patients who were pathologically and clinically diagnosed as primary pulmonary lymphoma between September 1995 and June 2003.
Results: There were 13 patients with MALT lymphoma and two with MALT lymphoma accompanied by large B-cell lymphoma, seven with diffuse large B-cell lymphoma and two with anaplastic large cell lymphoma. Half the patients were asymptomatic at presentation; 46% had respiratory symptoms and 16.7% had B-symptoms. Initial radiological findings were variable including nodules, masses, infiltrates or consolidation. The majority of patients (66.7%) needed surgical approaches (open thoracotomy or video-assisted thoracoscopy) for definite diagnosis. Bronchoscopy was performed in 83%, but only 30% showed a diagnostic yield. The 13 patients with MALT lymphoma were treated with a variety of modalities such as observation, surgery and single or combination chemotherapy, and combination chemotherapy was administered to 11 patients with non-MALT lymphoma regardless of surgery. The overall survival rate at 3 years for all 24 patients was 86% with a median follow-up of 32 months.
Conclusion: Although this entity of lymphoma appears to have a good prognosis, further clinical experience and long-term follow-up are needed to identify prognostic factors.

Key words: lung – MALT lymphoma – non-Hodgkin's lymphoma

INTRODUCTION

The most common extranodal site of presentation for non-Hodgkin's lymphoma (NHL) is the gastrointestinal tract, including stomach. Primary NHL of the lung is very rare, accounting for only 0.4% of all malignant lymphomas (1).

Primary pulmonary NHL is most commonly represented by marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type (MALT lymphoma) (1–3). Their development depends on MALT of the bronchus that is thought to be acquired as a result of chronic antigenic stimulation such as smoking, autoimmune disease or infection (1). They usually pursue indolent courses, remaining localized to the lung for long periods before dissemination (4,5). Treatment options are various, ranging from close observation to radiation, surgery or combination chemotherapy (1,5–7).

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Aggressive pulmonary NHL is less frequently detected and may arise from the transformation of an indolent lymphoma or occurs in individuals with an underlying disorder (e.g. immunodeficiency) (1,7). These patients generally require aggressive treatment with combination chemotherapy and prognosis seems to be worse than for low-grade MALT lymphoma (1,7,8).

Although there have been a few sporadic reports about primary pulmonary lymphoma of the lung (1,9), clinical features, optimal treatment and prognostic factors were not well defined. The objectives of this paper are to describe clinical features and therapeutic experience regarding patients with primary NHL of the lung.

METHODS

Patient Selection

We retrospectively reviewed the medical records of 42 patients with proven malignant lymphoma on pathological examination

of the lung tissue between September 1995 and June 2003. We used the following criteria (1,3) to diagnose primary pulmonary lymphoma: unilateral or bilateral pulmonary involvement with NHL; no evidence of mediastinal adenopathy; no evidence of extrathoracic disease by clinical staging work-up that includes thorough physical examination, computed tomographic scans of the chest, abdomen and pelvis and the examination of bilateral bone marrow biopsy specimens; no past history of lymphoma; no evidence of extrathoracic disease up to 3 months after the initial diagnosis. We included patients who were accompanied by hilar lymphadenopathy or adjacent chest wall invasion. Twenty-four patients who fulfilled the suggested criteria were enrolled for this study. Eighteen patients were excluded because of secondary pulmonary involvement with lymphoma (12 patients), extrathoracic involvement including bone marrow (four patients) and extrathoracic disease detected within 3 months after the initial diagnosis (two patients).

The following clinical data were abstracted from the medical records of each patient: demographic findings, presenting signs and symptoms, past medical history, chest radiographic findings at the time of diagnosis, diagnostic procedures, histology and stage of the tumor, treatment modality, follow-up data and survival. Patient follow-up was done through office visits or telephone interview.

Histology, Immunohistochemical and Molecular Genetic Study

The histology of primary pulmonary NHL was evaluated by two pathologists using the WHO classification (10). Immunophenotyping studies were performed to support the accurate diagnosis using antibodies to Ki-67, CD3, CD5, CD10, CD19, CD20, CD22, CD23, CD45 and CD79a selectively according to suspected subtype. Supplemental immunohistochemical staining using antibodies to CD4, CD8, CD21, CD30, CD43, CD56, cyclin-D1, BCL-2, BCL-6, epithelial membrane antigen (EMA), anaplastic lymphoma kinase (ALK) and immunoglobulin was performed in selected cases when initial phenotyping failed to support definitively the specific diagnosis or T-cell lymphoma was suspected. Finally, when the morphological features and immunophenotypic findings were inconclusive, a molecular genetic study was carried out to detect rearrangements of the immunoglobulin genes or T-cell receptor genes.

Response Criteria and Statistical Analysis

Demographic and clinical data were described with means ± standard deviation (SD) or medians, frequencies and percentages and compared using the Mann–Whitney test or Fisher's exact test. Complete response (CR) and partial response (PR) were evaluated according to international criteria (11). Survival duration was measured from the time of diagnosis to the date of death or the last follow-up. Overall survival was estimated using the Kaplan–Meier method. The survival rate between the MALT lymphoma and non-MALT lymphoma groups was compared by a log-rank test. A P-value of <0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics (Table 1)

The patients consisted of 15 male (62.5%) and nine female patients, with a median age of 59 years (range, 28–69 years). Ten patients (41.7%) were active or former smokers. Three patients had diffuse interstitial lung disease, one had diffuse panbronchiolitis and one had rheumatoid arthritis (RA).

At the time of diagnosis, 12 patients (50%) were asymptomatic. Eleven patients (46%) had respiratory symptoms and three of them also had B-symptoms and one had newly developed angioedema. One patient was initially seen with fever of unknown origin (FUO).

Radiological Findings and Diagnostic Procedures (Table 2)

The radiological findings were various, including single or multiple nodules in seven patients (29.2%), mass or masses in four (16.7%), infiltrates in 10 (41.7%) and consolidation in five (20.8%). Five patients had hilar lymphadenopathy and one had a direct chest wall invasion.

The pathological diagnosis was obtained with video-assisted thoracoscopic (VATS) wedge resection in 10 patients (41.7%)

Table 1. Demographic and clinical characteristics in 24 patients

	MALT lymphoma (n = 13)	Non-MALT lymphoma (n = 11)	P-value	Total (n = 24)
Age				
Mean (years) (range)	58.4	50.4	0.150	54.7 (28–69)
⩾60 years	7	4	0.444	11 (46%)
Sex				
Male	7	8	0.423	15 (62.5%)
Female	6	3		9 (37.5%)
Smoking	6	4	0.697	10 (41.7%)
Mode of presentation				
No symptoms	8	4	0.207	12 (50%)
Respiratory symptoms	4	7	0.217	11 (46%)
Cough/sputum	2	3		5 (20.8%)
Dyspnea	2	2		4 (16.7%)
Chest pain	0	2		2 (8.3%)
Hemoptysis	1	0		1 (4.1%)
B-symptoms	1	3	0.300	4 (16.7%)
LDH > normal level	1	5	0.048	6 (25%)
β_2-MG (mg/l) (mean ± SD)	1.78 ± 0.54	2.62 ± 0.86	0.039	2.25 ± 0.84

MALT, mucosa-associated lymphoid tissue; LDH, lactate dehydrogenase; β_2-MG, β_2-microglobulin; SD, standard deviation.

Table 2. Radiographic findings and diagnostic procedures for the 24 patients

	MALT lymphoma (n = 13)	Non-MALT lymphoma (n = 11)	Total (n = 24)
Radiological findings			
Unilateral lesion	7	5	12 (50%)
Right/left	5/2	3/2	8/4
Nodule or mass:	4	7	11 (46%)
Single/multiple	2/2	4/3	6/5
Infiltrates	6	4	10 (41.7%)
Consolidation	4	1	5 (20.8%)
Hilar adenopathy	1	4	5 (20.8%)
Chest wall invasion	0	1	1 (4.2%)
Diagnostic procedures			
Percutaneous biopsy	1	1	2 (8.3%)
Bronchoscopy	10	10	20
Biopsy	1	3	4 (16.7%)
TBLB	1	1	2 (8.3%)
Not diagnostic	8	6	14
VATS	6	4	10 (41.7%)
Open thoracotomy	4	2	6 (25%)
Wedge resection	1	0	1
Segmentectomy	0	0	0
Lobectomy	3	2	5
Pneumonectomy	0	0	0

MALT, mucosa-associated lymphoid tissue; TBLB, transbronchial lung biopsy; VATS, video-associated thoracoscopy.

and open thoracotomy in six (25%) (wedge resection in one, lobectomy in five). Although 20 patients received bronchoscopic examination, only six patients had definitive diagnosis: four by direct biopsy and two by transbronchial lung biopsy (TBLB). Two patients were diagnosed by ultrasono-guided percutaneous biopsy.

Histological Diagnosis Using WHO Classification

Extranodal marginal zone B-cell lymphoma of MALT type was found in 13 patients (54.2%). Nine patients including two who had MALT lymphoma accompanied by large B-cell lymphoma were diagnosed as diffuse large B-cell lymphoma (DLBL). In the remaining two patients, anaplastic large cell lymphoma (ALCL) was detected.

In brief, the tumor cells of MALT lymphoma were immunohistochemically CD20+, CD79a+, CD5−, cyclin D1−, CD10−, CD23+ and could be differentiated from benign lymphoid infiltrates by the presence of immunoglobulin gene rearrangement in four cases. The tumor cells of ALCL in this study were positive for CD30, EMA and ALK in addition to one or more of T-cell antigens such as CD3, CD4, CD5 and CD8. DLBL expressed more than one of various pan B-markers such as CD19, CD20, CD22, CD79a and immunoglobulin. Two cases of DLBL were positive for BCL-6 and one case expressed BCL-2. Another two cases were positive for CD10. However, they could be discriminated from follicular lymphoma by specific histological findings and clinical features.

Treatment

Three patients with asymptomatic MALT lymphoma did not receive any treatment initially while periodic follow-up was provided. One of them, however, received chemotherapy due to disease progression 6 months after diagnosis. All the patients received chemotherapy in the Samsung Medical Center. Three MALT lymphoma patients who received complete tumor resection are being contacted without adjuvant treatment. Single-agent chlorambucil (6 mg/day, p.o. for 6 months) or CVP (cyclophosphamide 1000 mg/m^2 i.v. day 1, vincristine 1.4 mg i.v. day 1, prednisolone 100 mg p.o. days 1–5, which were planned to be repeated every 21 days to six cycles) were administered to eight patients with MALT lymphoma including one who had disease progression after initial observation. Two patients with MALT lymphoma and DLBL, seven DLBL patients including two who underwent complete resection and two ALCL patients were treated with CHOP (cyclophosphamide 750 mg/m^2 i.v. day 1, doxorubicin 50 mg/m^2 i.v. day 1, vincristine 2 mg i.v. day 1, prednisolone 100 mg p.o. days 1–5, which were planned to be repeated every 21 days to six cycles).

Response and Survival

Two of three patients with watchful waiting initially are being followed up without treatment for 27 and 44.3 months, respectively. All eight patients with MALT lymphoma who received primary chemotherapy enjoyed objective response (CR in five, PR in three). Three of those achieving CR and three with complete tumor resection are still in a disease-free state with a median follow-up of 54 months (range, 8.6–94 months). The remaining two patients with CR were dead at 25.5 and 75 months (due to stroke in one and disease relapse in the other).

Of nine patients with DLBL, seven achieved CR with initial chemotherapy and one obtained PR with salvage treatment after showing progression to the first-line chemotherapy. The remaining one patient died of sepsis after the second course of CHOP. Of seven patients who achieved CR, five are still in first CR after a median follow-up of 39 months (range, 11–64.4 months) and two died at 6 and 43 months (due to disease relapse in one and unknown cause in another). Of two ALCL patients, one achieved CR which is currently disease-free at 34.5 months and another died of refractory disease 5 months after diagnosis.

For all 24 patients with primary pulmonary NHL, the overall survival rate at 3 years was 86% with a median follow-up of 32 months (range, 1.7–94 months) (Fig. 1).

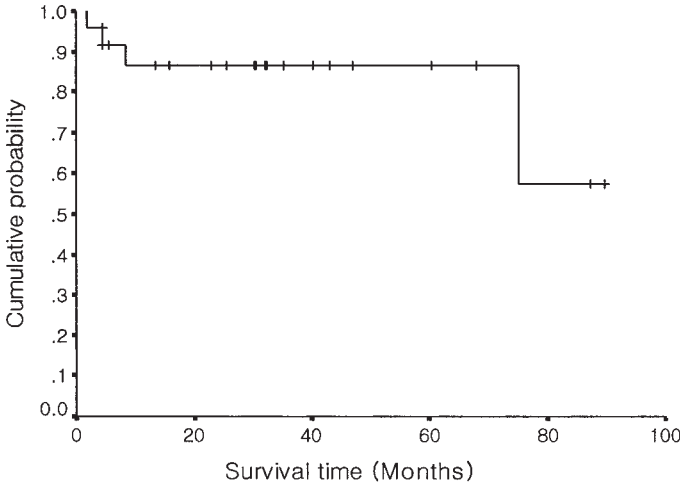

Figure 1. Overall survival of all 24 patients with primary pulmonary NHL.

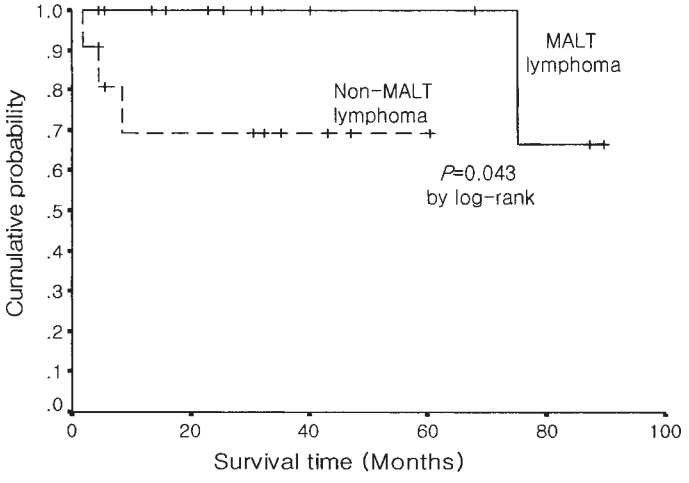

Figure 2. Overall survival comparison of MALT lymphoma with non-MALT lymphoma.

Comparision of Malt Lymphoma with Non-Malt Lymphoma (Table 1, Fig. 2)

There were no significant differences between MALT lymphoma and non-MALT lymphoma (MALT lymphoma accompanied by DLBL, DLBL or ALCL) in demographic features. With regard to the mode of presentation, there was also no significant difference between two groups ($P = 0.207$ for no symptoms, $P = 0.300$ for B-symptoms). The rate of patients with lactate dehydrogenase (LDH) above the normal level and the serum level of β_2-microglobulin were significantly higher in the non-MALT lymphoma group ($P = 0.048$, $P = 0.039$). Overall survival in the MALT lymphoma group was superior to that in the non-MALT lymphoma group ($P = 0.043$).

DISCUSSION

Although the lung is a relatively frequent site of secondary involvement of malignant lymphoma with an incidence of 25–40%, primary NHL of the lung is very rare (1). Therefore, it is difficult at present to find any reports characterizing this entity of malignant lymphoma except a few on MALT lymphoma of the lung (3,12). However, the actual incidence of primary pulmonary NHL might be higher than those reported, because diseases such as pseudolymphoma, lymphoid interstitial pneumonitis and lymphomatoid granulomatosis are morphologically difficult to distinguish from malignant lymphoma (13).

The most common primary lymphoma of the lung is low-grade MALT lymphoma arising from MALT of the bronchus (13,14). Since the presence of MALT in the lung was first described formally in 1973 (15), most authors believe that MALT is not a normal element of the lung but rather acquired secondarily in the long-term response to various antigenic stimuli such as smoking, immunological disease or chronic infection, e.g. in the stomach and the thyroid gland (1,12). In this review, MALT lymphoma represented 54% of all primary NHL of the lung, a rate similar to that reported by others (1). Of these patients, five had chronic inflammatory lung disorder such as diffuse interstitial lung disease, diffuse panbronchiolitis or RA.

Other types of malignant lymphoma localized to the lung are less frequently detected. In a review with 48 patients, DLBL was most common, comprising 28% of primary pulmonary NHL (1). In our study, nine patients (37.5%) had DLBL (two of them had both MALT lymphoma and DLBL). We also experienced ALCL, primary systemic type in the remaining two patients. This category of lymphoma, which is a recently recognized subtype of the peripheral T-cell lymphoma, is unusual and characterized by the expression of CD30 antigen (16). Because the usual clinical feature is peripheral lymphadenopathy with mediastinal sparing or extranodal disease with the skin as the most common site (17), primary pulmonary ALCL is very uncommon.

With regard to clinical features, half the patients were asymptomatic at presentation and especially in cases of MALT lymphoma, 61.5% of patients had no pulmonary or constitutional symptoms. Four patients (one with MALT lymphoma and three with non-MALT lymphoma) complained of B-symptoms and one of them was seen with FUO. The radiographic appearance of primary pulmonary lymphoma showed a variety of findings such as nodule or mass (single or multiple), ill-defined infiltrates or consolidation without any dominant feature. This suggests that any radiological abnormality of the lung parenchyma contains the possibility of lymphoma.

A large proportion of patients (66.7%) required surgical procedures to establish definitive diagnosis, by either open thoracotomy or VATS. Bronchoscopy was performed in 83%, but only 30% had a diagnostic yield via direct biopsy or TBLB. A few studies have suggested that a cell marker study or molecular techniques such as flow cytometry using bronchoalveoar lavage fluid may be helpful in diagnosing pulmonary lymphoma (12,18). In our cases, however, those studies were not performed. At present, we think that more invasive

approaches are still required for confirmatory diagnosis in many cases because there are a number of non-malignant reactive conditions that simulate malignant lymphoma.

Although there are several treatment options such as tumor resection, radiation, surgery followed by adjuvant treatment or chemotherapy alone, the therapeutic consensus has not been clearly established (1,5–7,12). In cases of asymptomatic MALT lymphoma with indolent clinical course, initial observation seems to be a reasonable option (7). We made a choice of watchful waiting for three patients with MALT lymphoma, with two of them being contacted without treatment for 27 and 44.3 months, respectively. For a MALT lymphoma patient who has symptoms or a desire for treatment, single-agent or combination chemotherapy can be considered. We administered single-agent chlorambucil or CVP to eight patients with MALT lymphoma as front-line chemotherapy. The result was that five patients achieved CR and three obtained PR. The role of surgery in the treatment of low-grade MALT lymphoma of the lung is not defined (1,7,12). In our review, three patients with complete resection were not administered adjuvant chemotherapy and are still disease free at 8.6, 20 and 72 months. Unlike MALT lymphoma, non-MALT lymphoma of the lung has been generally accepted as intermediate or high grade tumors showing worse prognosis (1,8). Because the rate of local recurrence after complete resection has been reported to be high (4,18), adjuvant chemotherapy or radiation therapy need to be considered for unfavorable non-MALT lymphoma. Regardless of whether a patient had surgery or not, we administered a CHOP regimen to all 11 patients with these types of lymphoma and achieved CR in eight patients including two who received complete resection.

Although there were a small number of patients in this review, we compared the demographic and clinical characteristics between MALT lymphoma and non-MALT lymphoma patients (including two with both MALT lymphoma and DLBL). There were no significant differences in the demographic features, the mode of presentation. However, the rate of LDH elevation and the serum level of β_2-microglobulin were significantly higher in the non-MALT lymphoma group, reflecting its potential role as a prognostic factor.

The prognosis of patients with primary pulmonary NHL is known to be relatively favorable. At the time of last follow-up, there were six cases of death among the total of 24 patients. Two deaths (one in MALT lymphoma and another in DLBL) were disease unrelated and four events (one in MALT lymphoma, two in DLBL and one in ALCL) were related to disease progression or treatment complications. The overall survival rate for all 24 patients was 86% at 3 years, which was comparable to that observed in another study (1). The overall survival was superior in patients with MALT lymphoma compared with those with non-MALT lymphoma ($P = 0.043$).

In conclusion, primary NHL of the lung is commonly presented as a non-specific abnormality on chest X-ray with no symptoms. For the majority of patients, surgical procedures such as VATS or open thoracotomy is still required to establish definite diagnosis. At present, there is no therapeutic consensus for these patients. Hence the treatment depends heavily on the presence of symptoms, the completeness of resection or the histological grade of lymphoma. This type of lymphoma, especially MALT lymphoma, appears to have a good prognosis. Further clinical experience and long-term follow-up are needed to identify prognostic factors.

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