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Bronchial-associated lymphoid tissue lymphoma: a clinical study of a rare disease ☆

Shahid Ahmed [a,*], Steven J. Kussick [b], Anita K. Siddiqui [c], Tawfiqul A. Bhuiya [d], Arfa Khan [d], Stephen Sarewitz [e], Harry Steinberg [d], Cristina P. Sison [f], Kanti R. Rai [d]

[a] *Saskatoon Cancer Center, University of Saskatchewan Campus, 20 Campus Drive, Saskatoon, SK, Canada S7N4 H4*
[b] *University of Washington Medical Center, Seattle, WA, USA*
[c] *Dartmouth General Hospital, Dalhousie University, Dartmouth, NS, Canada*
[d] *Long Island Jewish Medical Center, New Hyde Park, NY, USA*
[e] *Valley Medical Center, Renton, WA, USA*
[f] *North Shore-LIJ Research Institute, Biostatistic Unit, Manhasset, NY, USA*

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Abstract

Bronchial-associated lymphoid tissue (BALT) lymphoma is a distinct subgroup of low-grade B-cell extranodal non-Hodgkin's lymphoma, classified as marginal-zone lymphoma. This study was performed in order to assess the natural history of this rare entity. We evaluated retrospectively the clinical data of 22 patients with biopsy-proven BALT lymphoma at two tertiary-care institutions from 1996 to 2002. Immunophenotyping was done to confirm the abnormal populations of B-lymphoid cells in all cases, and clonality was determined by flow cytometry or molecular studies. There were 11 men and 11 women in the sample, median age 61 years (range 21–80 years); nine were asymptomatic at diagnosis. All 13 symptomatic patients had non-specific pulmonary complaints. On computed tomographic examination of the chest, 11 patients had bilateral disease, 12 had lung nodules, and 10 had a mass or air-space consolidation. In all but one case the disease was localised to the lung at diagnosis and none had peripheral blood or bone marrow involvement. Out of 22 patients, 20 received treatment in various combinations, 12 had chemotherapy and/or rituximab, six had surgery, and two received radiation therapy as primary treatment. A complete response (CR) was achieved in nine patients and a partial response was obtained in 10 patients. Seven of 10 patients who had unilateral disease achieved a CR. The estimated progression-free survival was 53 months. All patients were alive during the median follow-up period of 36 months (range 12–76 months). It appears that BALT lymphoma tends to be localised to lung at the time of diagnosis, responds well to local or systemic therapy, and has a favourable prognosis.

Keywords: BALT lymphoma; Pulmonary MALT lymphoma; Extranodal marginal-zone lymphoma; Lung; Non-Hodgkin's lymphoma

1. Introduction

Extranodal, marginal-zone, B-cell lymphoma (MZL) of mucosa-associated lymphoid tissue (MALT) types are a distinct subgroup of non-Hodgkin's (NHL) lymphoma that typically follow an indolent clinical course [1,2]. These lymphomas arise from a wide variety of extranodal sites, usually in the setting of chronic local inflammatory disorders or autoimmune diseases. The gastrointestinal tract is involved most frequently and accounts for more than two-thirds of the cases of extranodal MZL of MALT type [3,4]. Among the various non-gastrointestinal sites, the lung is one of the most frequent organs involved by extranodal MZL of MALT type [5–12]. Extranodal MZL of MALT type of the lungs arises from bronchial-associated lymphoid tissue (BALT), which is histologically distinct from true intrapulmonary lymph-node [13]. Although pulmonary

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* Corresponding author. Tel.: +1-306-655-2630; fax: +1-306-655-2639.
E-mail addresses: sahmed@scf.sk.ca, shahidahmed00@yahoo.com (S. Ahmed).

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extranodal MZL of MALT type or BALT lymphoma comprises more than two-thirds of all primary NHL of the lung, it is a rare entity and accounts for less than 1% of all lymphomas [5]. Because of their indolent clinical course and relatively benign histological features, BALT lymphomas have frequently been described using the term pseudolymphoma [12,14]. However, the recent advent of immunophenotyping and molecular genetic methods demonstrates that the majority of these tumours contain clonal populations of lymphoid cells, and are therefore likely to be true lymphomas. BALT lymphoma tends to remain localised in the lung for long periods of time, so the optimal clinical management, which would include abstaining from treatment, is not clearly defined. We here reviewed retrospectively the clinical data from 22 patients with low-grade BALT lymphoma evaluated at two tertiary-care institutions to assess the natural history of this rare entity.

2. Methods

After obtaining approval from institutional review boards at both hospitals, a computer-based search was performed and a total of 22 cases of biopsy-proven BALT lymphomas with complete clinical data were identified from 1995 to 2002. The diagnosis of BALT lymphoma was based on characteristic histological and immunophenotypical features of extranodal MZL of MALT type as classified by the International Lymphoma Study Group [1]. The pathology slides of lymphoma specimens were reviewed by a pathologist at each institution (SJK and TAB). Immunophenotyping was done in all cases by flow cytometry ($n = 16$) and/or immunohistochemical staining ($n = 9$) to confirm the abnormal populations of B-lymphoid cells. Clonality was determined using immunophenotyping by demonstrating light-chain restriction of the surface immunoglobulin on malignant cells and/or by molecular studies for immunoglobulin gene rearrangements ($n = 6$). Malignant cells were tested for CD20, CD5, and CD10 antigen expression. No cytogenetic studies were done. Cases of diffuse large B-cell lymphoma with background BALT lymphoma were excluded. The patients' records were reviewed and the following data collected: clinical symptoms, medical history, laboratory data, pulmonary function tests, and chest computed tomographic (CT) findings at the time of diagnosis, diagnostic procedure, staging information, treatment and follow-up. Staging included CT of the abdomen and pelvis ($n = 22$), positron-emission tomography (PET) or gallium scan ($n = 10$), and bone marrow biopsy ($n = 20$). No staging gastric endoscopy was performed.

A complete response (CR) was defined as no evidence of tumour by CT and/or PET scans. Duration of follow-up was calculated from the date of diagnosis to the last follow-up or the date of death. Since our study was retrospective and various treatment modalities were used, we defined progression-free survival from the time of diagnosis to the time at which there was a 25% increase in tumour size when no treatment was given, or to the time at which there was either a 25% increase in tumour size, or disease recurrence after achieving an objective response, in patients who received any treatment. Progression-free survival or time to first progression was analysed by the Kaplan–Meier method. Fisher's exact test was used to assess the correlation between the disease location and a CR, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical and laboratory features

The available clinical and laboratory features of patients with BALT lymphoma at the time of diagnosis are described in Table 1. None of these patients was known to be infected with human immunodeficiency virus. Four out of 22 patients had a history of immune disorders and/or a chronic inflammatory process. Among those four patients, two had common variable immune deficiency (CVID) with a history of recurrent upper and lower respiratory tract infections and one of these patients was also found to have lymphocytic interstitial pneumonitis by high-resolution CT scan (HRCT) and transbronchial lung biopsy. In the remaining two cases, one had history of chronic interstitial pneumonitis by

Table 1
Clinical and laboratory features of patients with BALT lymphoma

Features	$N = 22$ (%)
Median age at diagnosis	61 years (range 21–80 years)
Sex	
Male	11 (50)
Female	11 (50)
Smoking history	15 (68)
Associated immune and/or inflammatory process	4 (18)
No pulmonary or B symptoms	9 (41)
Pulmonary symptoms	13 (59)
Cough	8 (36)
Productive cough	4 (18)
Dyspnoea	4[a] (18)
Chest pain	2 (9)
B symptoms	3 (14)
Weight loss	2 (9)
Night sweats	1 (5)
Crackles on lung auscultation	7 (32)
Haemoglobin <120 g/l	1 (5)
Lactate dehydrogenase greater than normal	1/18 (6)

[a] In two of the 4 patients who had dyspnoea, it was thought to be related to their underlying obstructive lung disease.

HRCT and open lung biopsy, and clinically a diagnosis of sarcoidosis was made; the other had a mixed connective tissue disorder. Two out of 22 patients had a remote history of lymphoma. One patient with CVID had a history of stage 1 Hodgkin's disease 28 years before the diagnosis of BALT lymphoma, which was treated with radiation therapy; the other had a history of stage 1 diffuse large B-cell lymphoma 12 years before the diagnosis of BALT lymphoma, treated with chemotherapy. Both of these patients were in CR from their earlier lymphoma at the time of the diagnosis of BALT lymphoma. None had a reported history of extranodal MZL of MALT type. Nine out of 22 cases were asymptomatic and lymphoma was found incidentally on routine radiographic investigation. In the remaining 13 cases, non-specific pulmonary symptoms were the major presenting symptoms (Table 1). The median haemoglobin was 136.5 g/l (range 116–160 g/l). No patient had lymphocytosis. Serum protein electrophoresis was performed in 8 out of 22 patients and 1 patient had a biclonal gammopathy. Pulmonary function tests (PFT) were performed in 11 patients; they were abnormal in 9 patients. The most common PFT abnormality was obstructive airway disease (6 patients), followed by combined obstructive and restrictive airway disease (2 patients) and mild restrictive airway disease (1 patient).

3.2. CT features

CT scans of the chest were performed in all patients and CT findings are described in Table 2 (see Figs. 1 and 2). Lung nodules and air-space consolidation and/or mass were the major CT findings for BALT lymphoma in our series.

3.3. Diagnostic procedures

In symptomatic patients with BALT lymphomas, the median duration of symptoms before definitive diagnosis was 6 months (range 1–72 months). Two patients were treated with steroids and five received antibiotic treatment for presumptive non-resolving pneumonia. Nine patients had a history of previous biopsies and all had been transbronchial. The median delay between the first transbronchial biopsy and the diagnosis of BALT lymphoma was 3 months (range 0.5–36 months). These biopsies were either inconclusive or revealed an inflammatory process. For definitive diagnosis, surgical lung biopsy was performed in 14 patients (video-assisted thoracoscopy (VATS), $n = 9$; thoracotomy, $n = 5$), transthoracic lung biopsy in 5 patients, and transbronchial lung biopsy in 3 patients. Of those 14 patients who underwent surgical lung biopsy, eight had wedge resections or segmentectomy, and 6 had lobectomy. Five

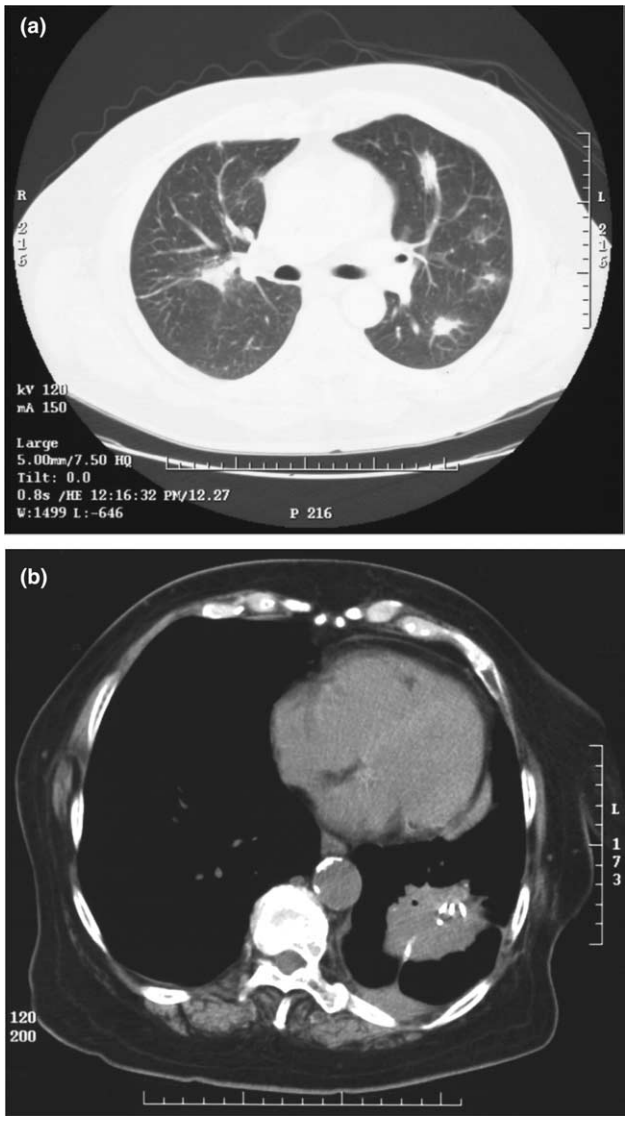

Fig. 1. (a) Bilateral lung nodules: CT scan shows bilateral multiple, irregularly shaped nodules. (b) Lung mass: CT scan shows a large irregular mass in left lower lobe with presence of punctate calcification. There is a pleural tag with adjacent plural thickening.

Table 2
Computed tomographic features of BALT lymphoma

Features	$N = 22$ (%)
Bilateral disease	11 (50)
Unilateral disease	11 (50)
Single lobe involvement	9 (41)
Lung nodule	12 (55)
Solitary nodule	5 (23)
Multiple nodules (Fig. 1(a))	7 (32)
Lung mass and/or air-space consolidation (Fig. 1(b))	10 (45)
Unilateral disease	5 (23)
Bilateral disease	5 (23)
Air-space consolidation with air Bronchogram (Fig. 2)	4 (18)
Patchy air-space and/or interstitial infiltrate	5 (23)
Peribronchial thickening	2 (9)
Hilar or mediastinal lymphadenopathy	1 (5)
Pleural effusion	2 (9)

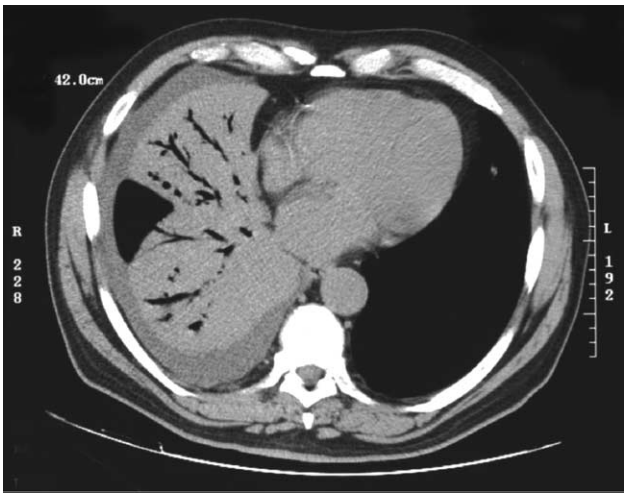

Fig. 2. Air-space consolidations: CT scan shows air-space consolidation with air bronchograms involving right middle and right lower lobe. Small adjacent pleural effusion is present.

patients had hilar and mediastinal lymph-node dissection. None had pneumonectomy.

3.4. Pathology and immunophenotyping

The tumour cells were small to medium-sized lymphocytes, either centrocytic or plasmacytoid-like, and tended to be admixed with plasma cells or scattered large-sized cells. No cases showed large-cell transformation. Characteristic lymphoepithelial lesions of MALT lymphoma were seen in 48% of cases. One case showed extensive local amyloid deposition in the lung. However, the patient did not have any monoclonal gammaglobulin in the serum. The other case revealed a sheet of histiocytic cells in association with BALT lymphoma.

Tumour cells were positive for CD20 expression and were negative for CD10 and CD5 expression. In one patient, no clonal B-cell population was identified by flow cytometry, but a small clonal B-cell population in a polyclonal background was identified by polymerase chain reaction (PCR) analysis. The patient had characteristic lymphoepithelial lesions and PCR for the *t*(14;18) characteristic of follicular lymphoma was negative. In all five cases where lymph-node dissection was performed, nodal involvement by BALT lymphoma was not revealed.

3.5. Staging

In all but one case the disease was localised to the lung at diagnosis. One patient had synchronous skin involvement by extranodal MZL of MALT type. No patient had peripheral blood or bone marrow involvement. CT of the abdomen and pelvis revealed splenomegaly in both patients with CVID, but one of them underwent splenectomy and pathological examination of the spleen did not reveal lymphoma. PET scanning, showed increased uptake of FDG in the lungs in all cases where it was done. No uptake was seen below the diaphragm except in a patient who had splenomegaly and underwent splenectomy.

3.6. Treatment and follow-up

Overall, 20 of the 22 patients were treated primarily with surgery ($n = 6$), radiation therapy ($n = 2$), or chemotherapy, and/or rituximab ($n = 12$), either alone or in various combinations. The various treatment modalities and the treatment responses are described in Table 3. The various chemotherapeutic regimens, with or without rituximab, used were as follows: CHOP (cyclophosphamide, adriamycin, vincristine and prednisone), $n = 4$; RCD (rituximab, cyclophosphamide and dexamethasone), $n = 2$; CVP (cyclophosphamide, vincristine and prednisone), $n = 3$; and RF (rituximab and fludarabine), $n = 4$. Rituximab was used alone or in combination with chemotherapy in 10 patients; 2 patients achieved a CR and eight had a partial response (PR). Nineteen of those 20 patients who received various treatments had an objective response. Nine patients achieved a CR, 10 had a PR, and one did not respond. Of those 9 patients who achieved CR, seven had unilateral disease and surgery was the primary modality of treatment in 6 patients and radiation therapy was primary treatment in the remaining 1 patient. The other 2 patients who achieved CR had bilateral disease, and both received chemotherapy with rituximab. 6 patients were initially observed for a median duration of 18 months (range 10–53 months). Four of those 6 patients ultimately received treatment due to progression of the disease. All were treated with chemotherapy and/or rituximab. One achieved a CR and three had a PR. Overall, of the 20 patients who were treated, seven out of 10 patients who had unilateral disease achieved a CR, compared to two out of 10 patients who had bilateral disease ($P = 0.06$).

Table 3
Treatment and response to therapy in patients with BALT lymphomas

Primary treatment	$N = 20$	Treatment response
Systemic chemotherapy ± R[a]	12	2 CR, 9 PR, 1 SD
Chemotherapy alone	2	2 PR
Rituximab alone	2	2 PR
Chemotherapy with rituximab	8	2 CR, 5 PR, 1 SD
Radiation therapy[b]	2	1 CR, 1 PR
Surgery[c]	6	6 CR

CR, complete response; PR, partial response; SD, stable disease.
[a] ±R, with or without rituximab.
[b] One patient received rituximab as adjuvant therapy after achieving CR.
[c] Two patients received adjuvant therapy, one received chemotherapy and another had rituximab.

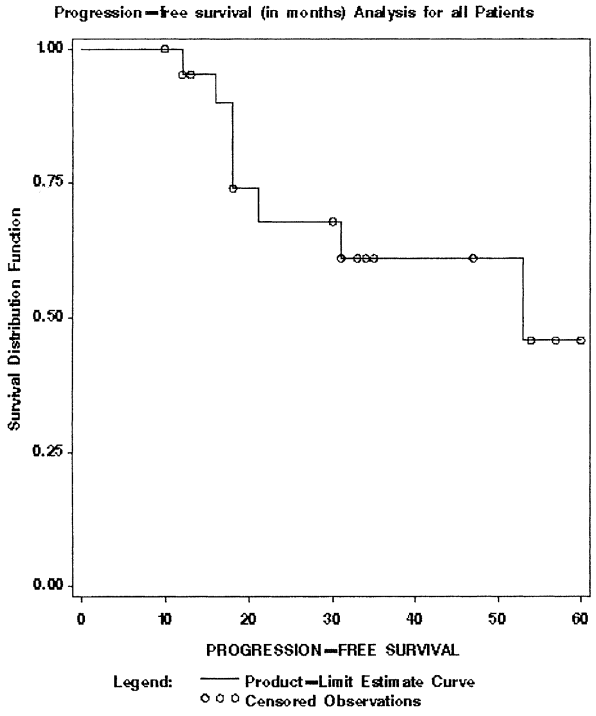

Fig. 3. The estimated progression-free survival of patients with BALT lymphoma.

After a median follow-up period of 36 months (range 12–76 months), all patients were alive. The estimated median progression-free survival time, or the time over which 50% of the subjects' disease had progressed, was 53 months (Fig. 3). In addition to 4 patients who had progression of the disease during the period of observation and ultimately received treatment, 3 patients who achieved a PR had progression of disease or relapse at other sites after a median follow up of 6 months (range 4–13 months). All were retreated with chemotherapy and/or rituximab. One patient who achieved a complete response had a relapse in the small bowel after 23 months.

4. Discussion

Our data confirm the previously described indolent behaviour of low-grade BALT lymphomas [5–10]. The median age of 61 years of our patients was similar to those of other series [8–11]. In contrast to the female preponderance in some series [6,11], we found an equal number of males and females. More than a third of the patients were asymptomatic and the pulmonary lesions were discovered incidentally on routine radiographic examination. All symptomatic patients had some non-specific pulmonary symptoms such as cough, dyspnoea and chest pain. A minority of patients had B symptoms. Clinical symptoms were similar in patients with bilateral and unilateral disease. Our series confirms the characteristic indolent clinical presentation of low-grade BALT lymphoma.

We found a high-incidence of immune disorders and/or chronic inflammatory diseases ($n = 4$) and smoking history ($n = 14$) in our studied population. Extranodal MZL of MALT type usually arises in sites normally devoid of lymphoid tissue, such as the stomach. Chronic antigenic stimulation, triggered by an autoimmune process or by persistent infection, is thought to stimulate the development of benign MALT at these sites. Similarly, many investigators believe that BALT is not a normal constituent of human lungs and rather its development is driven by long-term exposure to various antigenic stimuli [15,16]. The association of BALT with chronic lung inflammation has been described in conditions such as chronic hypersensitivity pneumonitis, diffuse panbronchiolitis, and various autoimmune diseases, such as rheumatoid arthritis [17–20]. Smoking has also been linked to the development of BALT. For example, by examining a total of 256 sites in 31 lungs Richmond *et al.* [21] demonstrated an increased BALT in smokers. However, smoking has not been clearly identified as a risk factor for BALT lymphoma and its role in the development of this condition in our patients remains speculative.

A high-incidence of bilateral disease was found at the time of diagnosis in our series. This is contrary to previous observations where BALT lymphoma was described predominantly as a unilateral disease [9,11]. In our series, despite a higher incidence of bilateral disease and the involvement of multiple lobes in unilateral disease, the disease was localised to the lungs at the time of diagnosis in nearly all cases. Pulmonary nodules and airspace consolidation with or without air bronchogram were the major CT abnormalities in our series. Pleural effusion and mediastinal or hilar lymphadenopathy was rare in our series, consistent with previous observations [8,9,11]. This suggests that the radiographic features of BALT lymphomas are non-specific and the radiographic presentation varies in different patients. BALT lymphoma should be considered in the differential diagnosis of non-resolving lung infiltrates or bilateral lung nodules. The rarity of pleural effusion and hilar or mediastinal lymphadenopathy in low-grade BALT lymphoma should raise the possibility of other malignancy or an inflammatory process in the presence of these radiographic abnormalities.

In one-third of the patients in our series the diagnosis of lymphoma was made by either transbronchial biopsy or radiologically guided transthoracic core-needle biopsy. In the remaining two-thirds of cases, VATS or thoracotomy was required for a definitive diagnosis, and these procedures also served a therapeutic purpose in many of these patients. Of note, 42% of patients had a history of earlier biopsies that were either inconclusive or revealed a benign inflammatory process. All these

biopsies were obtained by bronchosopy. The definitive diagnosis in these cases was obtained after a median delay of 3 months (range 5–36 months) when persistent symptoms or the increasing size of pulmonary infiltrates led to surgical lung biopsy.

Ferraro *et al.* [10] showed a low yield of bronchoscopy in primary non-Hodgkin's lymphoma of the lung. In their study the majority of lymphomas were BALT lymphoma. Out of 39 cases where a diagnostic bronchoscopy was performed, only 7 patients were diagnosed as having lymphoma-based on bronchoscopy. This finding suggests that surgical lung biopsy may be the procedure of choice for the definitive diagnosis of lymphoma in operable patients. Nonetheless, the ancillary immunohistochemical and molecular biological studies, by identifying the monoclonality of lymphoid cells, can be helpful when dealing with small samples obtained by less invasive procedures such as transthoracic or transbronchial biopsy [22,23].

Although extranodal MZL of MALT type are frequently localised at the time of diagnosis, they have tendency to disseminate among various MALT sites (20,97). Raderer *et al.* [24] have proposed an extensive staging procedure in patients with extranodal MZL of MALT type. CT scans of the chest, abdomen and pelvis, and bone marrow biopsy, are important staging procedures for determining the extent of the disease. The PET scan can be helpful in staging as well as to assess treatment response. An extensive invasive staging procedure, however, is not recommended in asymptomatic patients and none of the patients in our series had a staging endoscopic examination.

In agreement with previous observations, our data show the impressively favourable clinical course of BALT lymphoma regardless of the treatment. The optimal management of BALT lymphomas has not been clearly defined. However, as in our study, surgery appears to be very useful for localised low-grade BALT lymphoma and results in long-term disease control [5–11], whereas chemotherapy with rituxan appears useful in symptomatic patients or in patients with bilateral disease. Thus, in our series, unilateral disease correlates with a CR to therapy.

Strikingly, no mortality was recorded during the follow-up period. Disease progression was noted in 8 patients overall (36%), and four of them developed disease progression during the initial observation period. Our result is in agreement with most of the previous observations that show a slow rate of progression and a favourable course in BALT lymphoma, including 2-year and 5-year survivals of 100% and 95–84%, respectively [8,9,25]. However, it is worth noting that a single institutional study did report a significantly worse overall survival in patients with low-grade BALT lymphoma compared to age- and sex-matched control patients [11].

The optimal management of BALT lymphoma with regard to surgery, chemotherapy and radiation therapy alone or in combination, as well as abstention from therapy, is not defined. Surgery simultaneously serves both a diagnostic and a therapeutic purpose, and may be the treatment of choice for localised disease. Radiation therapy or single-agent chemotherapy can be used as alternative to surgery or as adjunctive treatment for incompletely resected disease. Watchful waiting for asymptomatic patients with surgically unresectable disease, or single-agent chemotherapy, are reasonable approaches. Combination chemotherapy may be considered in symptomatic patients with bulky or disseminated disease. In the absence of prospectively collected data, the therapeutic role of rituximab is not clear. However, as BALT lymphoma cells express CD20 antigen, the therapeutic possibilities of rituximab appear attractive and its use may be considered, alone or as an adjunct to other therapy.

In summary, our data confirm the indolent behaviour of BALT lymphoma. It tends to be localised to the lungs at the time of diagnosis and is associated with various immunological or inflammatory disorders and smoking. A third of patients may remain asymptomatic, with pulmonary lesions being incidentally discovered on chest radiography. In symptomatic patients, pulmonary symptoms are more common. Pulmonary nodules or airspace consolidation with air bronchograms are common radiographic findings. BALT lymphoma responds well to local or systemic treatment, and unilateral disease tends to correlate with a CR to local therapy.

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