

Does MALT Lymphoma of the Lung Require Immediate Treatment? An Analysis of 11 Untreated Cases with Long-term Follow-up

MARLENE TROCH¹, BERTHOLD STREUBEL², VENTZISLAV PETKOV³,
KARL TURETSCHKE⁴, ANDREAS CHOTT² and MARKUS RADERER¹

Departments of Internal Medicine I, Division of ¹Oncology and Cancer Center, and Internal Medicine IV, Division of ³Pulmology, ²Pathology and ⁴Radiology, Medical University of Vienna, Vienna, Austria

Abstract. *Background:* Mucosa-associated lymphoid tissue lymphoma (MALT lymphoma) of the lung is a relatively rare disease. As little is known about the natural clinical course if left untreated, all patients undergoing a watch-and-wait policy at our institution were investigated. *Patients and Methods:* A retrospective analysis identified a total of 11 patients with MALT lymphoma of the lung who did not undergo treatment following initial diagnosis. All patients had undergone extensive staging and were closely observed with restaging every three months. Histological assessment included immunohistochemistry for demonstration of the immunophenotype CD20+/CD5-/CD10-/cyclinD1-/CD23-. Genetic aberrations were assessed, using RT-PCR for t(11;18)(q21;q21) and fluorescence in situ hybridisation for the evaluation of t(14;18)(q32;q21), t(1;14)(p22;q32), trisomies 3 and 18. *Results:* Five patients had MALT lymphoma restricted to the lung, while the remaining six had additional extrapulmonary sites detected during staging. The median time of observation without therapy was 28.1 months (inter-quartile range: 5 to 60 months); within this time, all 11 patients showed at least stable disease. Six of these 11 patients, however, had spontaneous regressions and wax-and-wane phenomena of the pulmonary lesions, but not of extrapulmonary manifestations. Three of these patients had evidence of t(11;18)(q21;q21), while the remaining three had no evidence of genetic aberrations. One patient was referred for treatment after progression in the lung, while two patients experienced progression outside the lung. Currently, all patients are alive, with 8 patients still only being watched. *Conclusion:* Our findings suggest that MALT lymphoma of the lung is a

very indolent disease with the potential for spontaneous regression. In view of this, patients diagnosed with pulmonary MALT lymphoma might not require immediate treatment in the absence of symptoms and a watch-and-wait policy could be adopted.

Mucosa-associated lymphoid tissue lymphoma (MALT lymphomas) as initially described by Isaacson and Wright in 1983 (1) is a common type of lymphoma which accounts for 7% of newly diagnosed lymphomas at our institution (2). MALT lymphomas are most frequently diagnosed in the stomach and the gastrointestinal tract (3-5), but may occur at various extragastric sites. The most frequently encountered localisations are the salivary glands, where the occurrence of MALT lymphoma is thought to be associated with autoimmune diseases (5), and the ocular adnexa, where an association with *Chlamydia psittaci* has been described, albeit with large geographic variations (6, 7). The lung is also among the more common organs of origin, but no clear causal relationship with an inflammatory or infectious agent has been established so far, as opposed to the stomach or the salivary glands. Pulmonary MALT lymphoma, however, is often associated with the presence of a MALT lymphoma-specific genetic aberration, the t(11;18)(q21;q21) resulting in the *API2/MALT1* fusion transcript in about 50% of cases (8).

MALT lymphoma is generally thought to be an indolent disease with minor growth for a prolonged period of time and the potential for late dissemination (9). This is reflected by the generally good overall prognosis of patients, with median survivals not being reached in larger series even after up to 10 years (9-11). In addition, a recent prospective study has shown that dissemination at diagnosis apparently does not negatively influence prognosis and survival (12). Little, however, is known about the natural history of MALT lymphoma without therapy, as most patients either undergo *Helicobacter pylori* (HP) eradication for localized gastric MALT lymphoma or radiotherapy for early stage

Correspondence to: Markus Raderer, MD, Department of Internal Medicine I, Division of Oncology, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria. Tel/Fax: +43 1 40400 2296, e-mail: markus.raderer@meduniwien.ac.at

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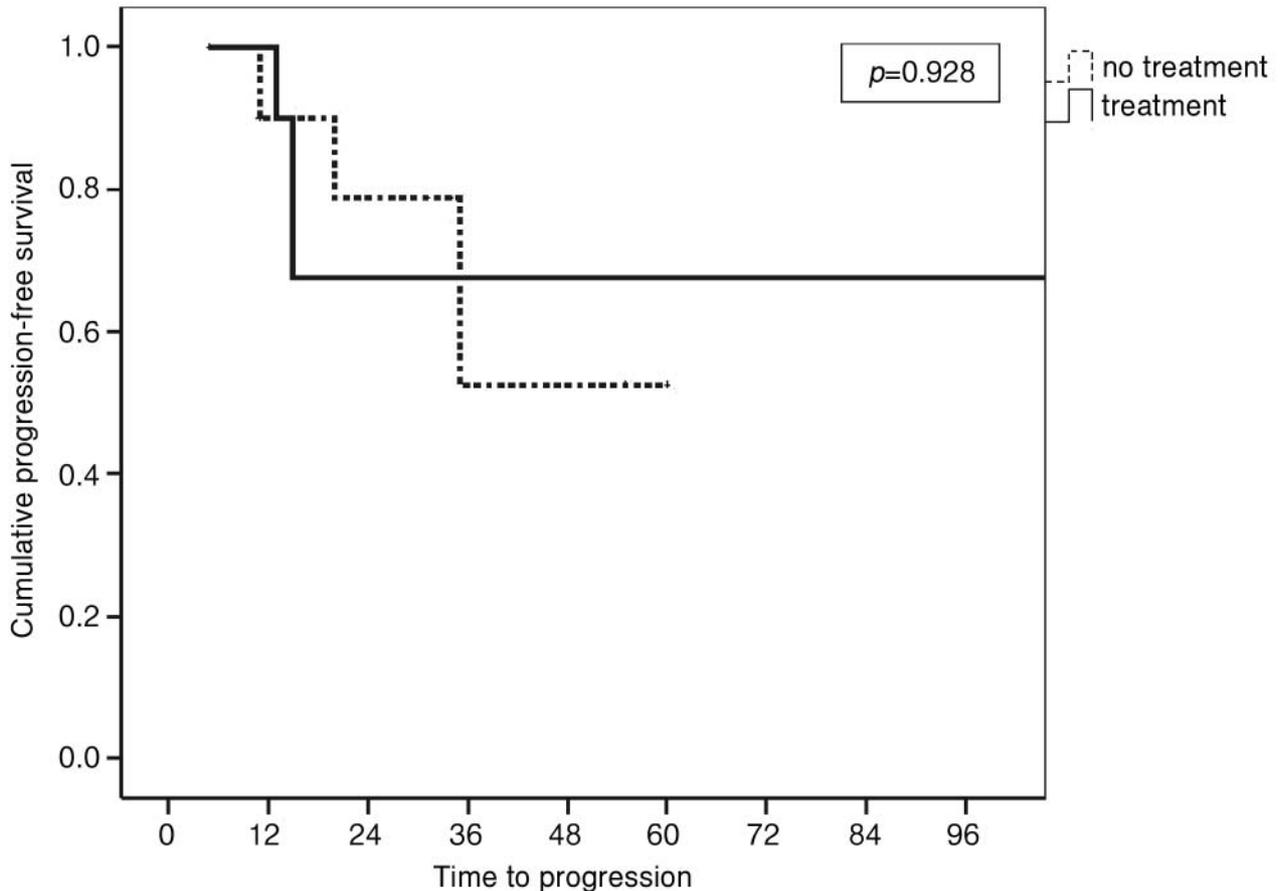


Figure 1. Time to progression in untreated vs. treated patients.

extragastric disease. The only exception in the current literature is a report on untreated ocular adnexal MALT lymphoma (13) demonstrating excellent outcome without any therapy also in localized disease.

Encouraged by the clinical course of a patient who showed spontaneous wax-and-wane phenomena of pulmonary MALT lymphoma lesions after refusing therapy, we retrospectively analysed the course of untreated pulmonary MALT lymphoma at our institution. In addition, we also assessed the clinical course and outcome of patients undergoing treatment during the same period.

Patients and Methods

A retrospective analysis of MALT lymphoma patients admitted at our institution between 1997 and 2006 disclosed a total of 11 patients with histologically verified MALT lymphoma of the lung undergoing no treatment for different periods of time following initial diagnosis. In addition, another 10 patients with pulmonary lymphoma underwent different forms of therapy during the same time span.

Out of these 11, 7 patients had refused treatment due to the absence of symptoms, while in two patients the high age along with coexisting severe diseases (coronary artery disease with bypass surgery) was decisive for observation only. One patient had multiple lesions in the lung which remained relatively unchanged for about three years before the patient was subjected to biopsy and diagnosed with MALT lymphoma. In the last patient, breast cancer with bone marrow involvement was detected in the course of diagnostic work-up for MALT lymphoma and the patient received tamoxifen as antihormonal treatment for receptor-positive breast cancer.

Biopsy samples obtained either by bronchoscopy or CT-guided fine needle biopsy were evaluated by a reference hematopathologist (A.C.) according to the criteria established by Isaacson and adopted in the recent WHO classification for MALT lymphoma. Immunological phenotyping on paraffin sections was carried out for demonstration of light-chain reaction and the CD20+/CD5-/CD10-/cyclinD1-/CD23- phenotype which is consistent with MALT lymphoma (14).

Analysis of MALT lymphoma-associated genetic aberrations was performed in all patients: t(11;18)(q21;q21) involving *API2* and *MALT1* was assessed by reverse transcription-PCR; t(14;18)(q32;q21) involving *IGH* and *MALT1*, t(1;14)(p22;q32) involving *BCL10* and

Table I. patient characteristics of wait and watch MALT lymphoma patients.

Gender	Age at diagnosis (years)	Extrapulmonary organ involvement	Bilateral involvement of the lung	Time of observation (months)	Regressions during the observation period	Referred for treatment	Autoimmune disease	Genetic aberration
Female	70	No	No	5	No	No	No	None
Male	40	Parotid, stomach, lacrimal gland	Yes	20	No	Yes	No	t(11;18)(q21;q21)
Female	56	No	Yes	56	Yes	No	No	t(11;18)(q21;q21)
Male	51	No	No	23	Yes	No	No	t(11;18)(q21;q21)
Female	54	Breast, parotid, orbita	No	15	Yes	No	SS*	Trisomie 3, 18
Female	88	No	No	5	No	No	No	None
Male	73	Colon	No	35	No	Yes	No	t(11;18)(q21;q21)
Male	82	Stomach, bone marrow	No	34	No	No	Hepatitis (a.i. *)	t(11;18)(q21;q21)
Female	53	No	No	60	Yes	Yes	No	None
Female	74	Stomach	No	13	Yes	No	No	t(11;18)(q21;q21)
Female	42	Parotid, conjunctiva	Yes	24	Yes	no	SS*	None

SS: Sjögren syndrome; a.i.: autoimmune hepatitis.

IGH, and trisomies 3 and 18 were investigated by fluorescence *in situ* hybridization as described elsewhere (8).

All patients underwent extensive staging according to our standardized procedure (12), consisting of ophthalmological and otorhinolaryngological examination with sonography/MRI of lacrimal and salivary glands, gastroscopy with multiple biopsies, endosonography of the upper GI-tract, enteroclysis, colonoscopy, CT scan of thorax and abdomen, and a bone marrow biopsy.

Restaging included CT scan of the thorax and abdomen every 3 months in all patients, while additional investigations were performed with regards to the site of involvement outside the lung. Apart from retrospectively analysing these 11 cases of untreated pulmonary MALT lymphoma, we have also compared their clinical course with 10 patients suffering from MALT lymphoma of the lung who were put on therapy in terms of time to progression using Kaplan-Meier plots (see Figure 1).

Results

A total of 11 patients (7 female; 4 male) with histologically verified MALT-lymphoma of the lung with a median age of 62 years (inter-quartile range (IQR): 40-88 years) at diagnosis and a median follow-up time of 28.1 months (IQR: 5-60months) were eligible for analysis (Table I). Five patients had MALT lymphoma restricted to the lung (with bilateral involvement in 3/5 cases), while six patients had multifocal disease. Two of these patients showed subclinical spread to the GI tract (one to the stomach, one to the colon) detected during staging, one to the stomach and bone marrow, one to the parotid, lacrimal gland and stomach, one to the parotid, breast and orbit and one to the

parotid and conjunctiva. All sites of lymphoma involvement had been histologically verified in our patients.

HP infection as well as hepatitis C was present in one patient each, and a concomitant autoimmune disease was found in three patients (Sjogren's syndrome in two patients and autoimmune hepatitis in one). In keeping with the literature, t(11;18)(q21;q21) was detected in 6 out of these 11 patients and one additional patient tested positive for trisomies 3 and 18.

Monoclonal gammopathy was found in 4/8 patients assessed, while the feature of plasmacytic differentiation, defined as light-chain restricted plasma cells growing in sheets, was found in 4 patients. One patient had both monoclonal gammopathy and plasmacytic differentiation.

In these eleven patients, no anti-lymphoma treatment (*i.e.* chemotherapy, radiation or antibody therapy) was administered during a median observation time of 28.1 months. Currently, all patients are alive with 8 still only being watched. Six of these 11 patients showed spontaneous regression, but not complete remission of the MALT lymphoma in the lung. In three of these patients, this was followed by at least one episode of increase, with consecutive regression (wax and wane) in the pulmonary lesions. Three of these patients had disease restricted to the lung, while the other three had more widespread dissemination of the lymphoma. Three of these patients had t(11;18)(q21;q21)-positive lymphomas, one had trisomy 3 and 18, while the other two patients had no detectable genetic aberrations. The time to regression was 6 to 60 months in these six patients.

Two of these patients had been given antibiotic treatment with clarithromycin due to cough and fever leading to diagnosis of the lymphoma. Following antibiotic therapy, symptoms resolved completely and no further therapy was administered in either case. One additional patient was given systemic prednisolone due to obstructive ventilation changes, as evidenced by pulmonary function tests, which was switched to inhaled steroids after two weeks, along with topical beta-mimetics. Another patient with disease restricted to the lung was watched for 60 months, with the lymphoma showing periods of wax and wane. He was referred for treatment due to the development of cough and episodes of post-stenotic pneumonia which could be controlled but not completely abrogated by antibiotic therapy.

In total, 3 patients were put on therapy, while the remaining 8 are continuing a watch-and-wait policy. All three patients on therapy showed progressive disease at 20, 35 and 60 months after diagnosis, respectively. Only one of them had progressive pulmonary lymphoma requiring therapy due to recurring infectious episodes, as already stated. In the other two patients, the tumor progressed outside the lung (appearance of new lesions in the colon and progression of synchronously diagnosed lesions in the lacrimal and parotid gland, respectively).

In the same observation period, between 1997 and 2006, 10 patients (3 female / 7 male) with MALT lymphoma of the lung were treated at our institution. As this was not a prospective analysis, various different therapy forms were applied in these patients. Nine patients underwent different forms of chemotherapy: four patients were given rituximab plus (CHOP)-chemotherapy, one patient was administered CHOP, one rituximab, one was treated with 2CdA, one with fludarabine and one with bortezomib. The remaining patient had surgery followed by radiation.

We have compared these two different groups with regards to median observation time, time to progression and overall survival. After a median follow-up time of 58 months (IQR: 13 to 168 months) one patient has died in the treated group, while none of the eleven untreated patients has died within the median follow-up time of 28 months. No significant difference was seen in terms of time to progression (Figure 1).

Discussion

Recent data from Japan (13) have shown that MALT lymphomas of the ocular adnexa follow a favourable course if no treatment is administered, even in patients with localized stages amenable to potentially curative radiation. In this retrospective analysis including 36 patients, 70% remained untreated due to the absence of symptoms/signs of progression after a median follow-up

time of 7.1 years. Apart from this report, however, no clear data exist on the clinical course of MALT lymphoma arising at other sites if left untreated.

Our series is the first to demonstrate that patients with pulmonary MALT lymphoma might not require immediate therapy following diagnosis. Although retrospective in nature, our data nevertheless suggest that MALT lymphoma of the lung is an indolent disease with minor growth over a prolonged period of time and late dissemination.

In our series, 11 patients initially presenting with MALT lymphoma of the lung were identified, with 5 patients having disease restricted to the lung. Six patients, however, were found to have asymptomatic manifestations outside the lung during meticulous staging. This is in contrast to a recent series of 22 patients reported by Ahmed and coworkers (15) who found all but one patient as having MALT-lymphoma restricted to the lung. Our extensive staging routine, however, along with the fact that all deposits detected by staging had been asymptomatic might account for the apparent discrepancy, as might potential geographic differences between the patient populations.

All of our eleven patients had at least stable lesions in the lung for a prolonged period of time which ranged between 5 and 56 months, irrespective of the stage of the disease. The survival and time to progression was not significantly different from a cohort of 10 patients undergoing therapy during the same period at our institution. As this was not a prospective study but a retrospective analysis, these data are merely a suggestion for the validity of a wait-and-see concept in patients with pulmonary MALT lymphoma as opposed to immediate therapy. In order to prove our hypothesis, a randomised trial with uniform treatment as opposed to wait-and-see until development of progression or symptoms would be required.

Interestingly, six of these 11 untreated patients had spontaneous regressions of the pulmonary lesions with wax-and-wane during follow-up. This phenomenon, however, was only seen in the lung, while extrapulmonary lesions present in some patients did not change significantly. This clinical behaviour was apparently not related to currently known genetic MALT lymphoma-specific aberrations, as three of these 6 patients had t(11;18)(q21;q21), one had trisomies 3 and 18, whereas no aberration was detected in the remaining two patients.

Of further interest however is the fact that two of these patients had undergone antibiotic therapy with clarithromycin due to febrile episodes and cough on lymphoma diagnosis. While one cannot rule out that an effect similar to that seen in gastric MALT lymphoma after HP eradication might have occurred, it is probably more likely that antibiotic treatment might have influenced the radiological appearance due to a decrease in concomitant inflammation. This hypothesis is further underscored by the

finding that one additional patient showed a slight decrease of pulmonary infiltrates after administration of systemic steroids which were then switched to inhalative medication, which might also have influenced an inflammatory component. As the radiological pattern of pulmonary MALT lymphoma is not very specific (16), and many patients are in fact misdiagnosed with nonspecific inflammatory disease before histological assessment due to persistent lesions, we think that this interpretation is more likely than a real regression of the lymphoma. On the other hand, our findings of repeated changes in lesion size suggest that a single evidence of pulmonary progression in the absence of symptoms does not justify immediate treatment, as this might also constitute an inflammatory phenomenon with the potential to resolve spontaneously.

Taken together, our data suggest that primary MALT lymphomas of the lung have a very minor growth with a stable size for a prolonged period of time. In the absence of symptoms, such patients might probably be candidates for a watch-and-wait policy without the requirement for immediate (and potentially aggressive) therapy. Prospective studies on this topic are warranted to assess whether immediate therapy in asymptomatic patients is indeed beneficial.

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