Treatment of Mucosa-associated Lymphoid Tissue Lymphoma in Sjögren's Syndrome: A Retrospective Clinical Study

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ABSTRACT. ***Objective.*** To retrospectively analyze the clinical course of patients with mucosa-associated lymphoid tissue (MALT)-type lymphoma of the parotid gland and associated Sjögren's syndrome (SS).

Methods. All consecutive patients with SS and MALT lymphoma (MALT-SS) diagnosed in the University Medical Center Groningen between January 1997 and January 2009 were analyzed. Clinical course and treatment outcome of SS and MALT lymphoma were evaluated.

Results. From a total of 329 patients with SS, 35 MALT-SS patients were identified, with a median followup of 76 months (range 16–153 mo). MALT lymphoma was localized in the parotid gland in all cases. Treatment consisted of "watchful waiting" (n = 10), surgery (n = 3), radiotherapy (n = 1), surgery combined with radiotherapy (n = 2), rituximab only (n = 13), or rituximab combined with chemotherapy (n = 6). Complete response was observed in 14 patients, partial response in 1 patient, and stable disease in 20 patients. In 6 of 7 patients with initially high SS disease activity (M-protein, cryoglobulins, IgM rheumatoid factor > 100 KIU/l, severe extraglandular manifestations), MALT lymphoma progressed and/or SS disease activity increased after a median followup of 39 months (range 4–98 mo), necessitating retreatment. Only 1 patient with MALT who had low SS disease activity showed progression of lymphoma when left untreated.

Conclusion. An initially high SS disease activity likely constitutes an adverse prognostic factor for progression of lymphoma and/or SS. Such patients may require treatment for both MALT lymphoma and SS. In SS patients with localized asymptomatic MALT lymphoma and low SS disease activity, a "watchful waiting" strategy seems justified. (J Rheumatol First Release Aug 15 2011; doi:10.3899/jrheum.110077)

Key Indexing Terms:
MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMA SJÖGREN'S SYNDROME

Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by chronic inflammation of the salivary and lacrimal glands. SS is frequently accompanied by systemic symptoms. Four percent to 7%[1,2] of patients with SS develop malignant B cell lymphoma, 48%–75% of which are of the mucosa-associated lymphoid tissue (MALT)-type. These B cell lymphomas are most frequently located in the parotid gland[3,4,5]. A study showed a 6.6-fold increase of non-Hodgkin's lymphoma (NHL) in patients with SS compared to controls[6]. MALT lymphoma of the parotid gland was almost exclusively associated with SS, as there was a 1000-fold increase in the relative risk of having SS in the case of a MALT lymphoma presenting in the parotid gland[6]. In patients with SS, parotid gland enlargement is frequently present but varies in time. The change from variable to persistent enlargement of glands is an important clinical sign, indicating the possible development of MALT lymphoma. Further, the emergence of lymphoma in SS may be heralded by extraglandular manifestations of SS (e.g., palpable purpura, vasculitis, renal involvement, peripheral neuropathy). None of these features is specific for MALT lymphoma in SS, but any of them should raise suspicion, particularly if accompanied by features such as monoclonal gammopathy, reduced levels of complement C4, CD4+ T lymphocytopenia, a sharp increase in IgG levels, or cryoglobulinemia[2,7,8,9,10].

Assessment of SS patients who may have developed a MALT lymphoma is not always easy, but an incisional biopsy of the parotid gland can safely be performed under local anesthesia[11].

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MALT lymphoma in general is an indolent disease, with a reported 5-year overall survival between 86% and 95%, without significant difference in clinical course between localized and disseminated disease[12,13]. Recurrences may involve extranodal or nodal sites. Progression to aggressive lymphoma is rare, occurring in fewer than 10% of cases[14].

MALT lymphoma in patients with SS is often localized at 1 or more salivary glands [usually the parotid gland(s)], but can also occur in other extranodal sites, such as the orbital adnexa[15] and stomach[16]. Dissemination of MALT-SS may be observed in local draining lymph nodes or sometimes distant nodes, and occasionally other mucosal sites and bone marrow[17]. Prognosis does not seem to be influenced by dissemination to other MALT organs, although involvement of lymph nodes might be an adverse prognostic factor[13,17].

The relative infrequency and heterogeneity of MALT lymphomas, with their different biology, clinical presentation, and behavior, make it difficult to define optimal treatment of these patients in general. Antibiotics are widely used as initial treatment of MALT lymphoma associated with microbial pathogens, in particular gastric MALT lymphoma associated with *Helicobacter pylori*[18,19,20,21]. In other MALT lymphomas with symptomatic local disease, local treatment (surgery or radiotherapy) results in excellent disease control[22]. However, in patients with SS, conventional radiotherapy of the salivary glands (25 to 39 Gy) may lead to significant further xerostomia[23,24]. An alternative approach might be low-dose 2 × 2 Gy involved-field radiotherapy. This therapy is very effective in follicular lymphoma[25] and data in MALT lymphoma seem promising[26,27]. For symptomatic disseminated disease, chemotherapy has commonly been used, with a 75% complete remission rate and 5-year event-free survival and overall survival rates of 50% and 75%, respectively[12,13,28,29,30]. More recently, rituximab, a chimeric murine/human anti-CD20 monoclonal antibody that is highly efficacious in patients with B cell lymphoma, alone or in combination with chemotherapy[31,32,33,34], has also been used effectively in patients with MALT lymphoma, with or without associated SS[35,36,37,38,39,40].

At present, no clear guidelines exist for the management of patients with MALT-SS. In this retrospective study we report our experience in 35 consecutive patients with MALT-SS treated in our center.

MATERIALS AND METHODS

Patients. Our hospital, the University Medical Center Groningen, is a referral institute for SS in The Netherlands. Patients are referred to either the Department of Rheumatology or Oral Medicine. Subsequently, all patients with suspicion of SS are routinely evaluated in both departments. In cases of MALT lymphoma, patients are also seen by a hematologist. A retrospective analysis was performed of all consecutive patients diagnosed with SS and MALT lymphoma in our hospital, between January 1997 and January 2009. Patients with a diagnosis of extranodal marginal zone (MALT) lymphoma according to the World Health Organization classification[41] and a concomitant diagnosis of SS according to the American-European consensus criteria[42] were included. All patients with MALT-SS were seen at 6-month intervals for routine followup. Followup ended February 1, 2010 (median followup 76 mo, minimal followup of 12 mo).

Diagnosis of SS and MALT lymphoma. A complete routine diagnostic investigation for SS was carried out in all patients at their first visit as described[38]. In brief, investigation included subjective complaints of ocular and oral dryness, eye tests (Rose bengal staining and Schirmer tear test), measurement of unstimulated whole salivary flow, parotid sialography, and serology (anti-SSA/SSB antibodies). In all patients an incision biopsy of the parotid gland was part of the investigation and was performed under local anesthesia[11,43]. All patients in our cohort were diagnosed using the SS classification criteria of the American-European consensus group; findings of hepatitis C and HIV infections were excluded accordingly[42].

All biopsies were reviewed by a hematopathologist (PMK). In all 35 cases immunohistochemistry was performed for at least CD3, CD5, CD20, CD79a, CD10, BCL6, and cytoplasmic immunoglobulins (kappa, lambda, IgM, IgG, and IgA). In 21/35 cases DNA analysis of clonality was performed using polymerase chain reaction (PCR) for FR1, FR2, and FR3 of the immunoglobulin heavy-chain gene complex, as described[44,45]. All FR PCR reactions were performed in 4-fold at 2 dilutions. All 21 cases revealed a dominant and reproducible monoclonal population of B cells in 1 or more framework PCR reactions. To distinguish between reactive benign lymphoproliferation and MALT lymphoma, the classification of Quintana, *et al*[46] was used. All lymphomas were classified according to the WHO classification of 2008[41].

Staging of MALT lymphoma and disease activity score of SS. Patients were staged according to a standard lymphoma protocol including computed tomography (CT) or magnetic resonance imaging (MRI) scans of head/neck, thorax, and abdomen, and a bone marrow biopsy[47]. For SS-associated MALT lymphomas located in the salivary gland, we used a relatively simple staging system based on the Ann Arbor classification[47] and the modification for primary gastric lymphoma by Musshoff[48] as follows: (1) Localized disease: lymphoma located in 1 or more salivary glands (unilateral or bilateral), without enlargement of lymph nodes. (2) Locally disseminated disease: lymphoma localized in 1 or more salivary glands (unilateral or bilateral) with 1 or more enlarged regional lymph nodes (> 1 cm). (3) Disseminated disease: localization of lymphoma in 1 or more salivary glands (unilateral or bilateral) with 1 or more enlarged distant lymph nodes (> 1 cm), and/or bone marrow, spleen, liver, or other extranodal site than the salivary gland, or localization of lymphoma in multiple extranodal sites.

SS disease activity was evaluated based on the following variables: the presence of extraglandular manifestations (e.g., arthritis, fatigue, vasculitis, glomerulonephritis), subjective sicca symptoms (using a 100-mm visual analog scale), salivary gland function, and serological measures [levels of total IgG and IgM rheumatoid factor (RF), C4, cryoglobulins, M-protein]. Based on these measures, a global impression of disease activity (low, moderate, high) was determined by the physicians (RPEP, JP, HB, FKLS, GWvI) participating in the multidisciplinary group for patients with SS and MALT lymphoma.

Treatment and treatment evaluation. The choice of treatment modality was decided by a team of experts (rheumatologist, oral surgeon, pathologist, hematologist) based on clinical, serological, and radiographic data. In general the following treatment regimens were used: watchful waiting, surgery, radiotherapy, or surgery combined with radiotherapy or cyclophosphamide-prednisone. Rituximab was available from 2002 onward and was added to the treatment regimens. Rituximab monotherapy was given as 4 infusions of 375 mg/m^2 given once weekly as described[38]; rituximab with cyclophosphamide and prednisone (R-CP) was given as 6–8 intravenous infusions of 375 mg/m^2 of rituximab and 750 mg/m^2 of cyclophosphamide. One infusion was given every 3–4 weeks, in combination with 100 mg prednisone PO for 5 days. After initial rituximab or R-CP treatment, no maintenance immunotherapy was given.

Data on time between diagnosis of SS and presentation of lymphoma, response to treatment, and clinical course during followup were retrieved from the medical records. Tumor responses were classified as complete

response (CR), partial response (PR), stable disease (SD), or recurring/progressive disease (PD), according to the standardized response criteria for malignant lymphomas[49,50]. In brief, CR required the absence of palpable swelling of salivary glands and reduction of size of all nodes to < 1 cm on computed tomography/magnetic resonance imaging (MRI), and normalization of bone marrow, spleen, liver, or other extranodal sites, if initially involved. In patients with localized disease, CR was considered when no evidence of disease was present after diagnostic surgical excision with or without subsequent radiotherapy or after R-CP objectified by MRI. Seven patients treated with rituximab monotherapy took part in a prospective clinical trial in which a repeated parotid gland biopsy was performed after treatment as defined by protocol[38]. In these patients, a repeated biopsy of the involved parotid gland had to show complete disappearance of the lymphoma infiltrate in order to classify them as having achieved CR. PR required regression of initial tumor mass by ≥ 50% without development of new lesions. SD was defined as < 50% regression or < 50% increase of the known sites of disease. PD recurrence required ≥ 50% increase of any previously identified abnormal lesions or any new lesion (including recurrence in case of previous CR), irrespective of simultaneous responses at other sites.

Since there are no validated disease activity response criteria for SS[51,52], deterioration of SS was arbitrarily defined as the occurrence of 1 or more of the following: an increase in levels of IgG, increase in levels of IgM-RF, decrease in salivary gland function, increase in subjective oral or ocular symptoms, and/or the development of extraglandular manifestations (arthritis or vasculitis; pulmonary, hepatic, or renal SS involvement). Improvement of SS required 1 or more of the following: a decrease in levels of IgG and/or IgM-RF, improvement of salivary gland function[53], improvement of subjective symptoms, and/or disappearance of extraglandular manifestations. Stable disease was defined as the absence of deterioration or improvement according to the criteria noted above. The criteria are in agreement with the outcome criteria for SS for clinical trials as proposed by Pillemer, *et al*[54] and the disease activity scales that were developed later and remain to be validated[51,52].

RESULTS

Patient characteristics. From a total of 329 patients with SS diagnosed in our hospital between January 1997 and January 2009, 35 (11%) patients with MALT-SS were identified. Two SS patients developed extraglandular lymphoproliferative malignancies without parotid gland involvement; 1 patient had an inguinal extra-ossal plasmacytoma, the other a rectal MALT lymphoma. These patients were both excluded from analysis. Characteristics of MALT lymphoma and SS of the 35 patients in the study are listed in Tables 1 and 2.

Table 1. Clinical characteristics of the 35 patients with MALT-SS. See Materials and Methods for definitions of MALT-SS staging and SS disease activity.

Characteristic	No. Patients (%)
Male	3 (9)
Female	32 (91)
MALT staging	
Localized disease	26 (74)
Locally disseminated	5 (14)
Disseminated disease	4 (11)
SS disease activity	
Low	28 (80)
High	7 (20)

In 11 (31%) out of 35 patients, MALT lymphoma was detected in a parotid biopsy during routine diagnostic investigation of SS. Eighteen MALT lymphomas (51%) were detected in patients presenting with active SS and suspicion of MALT lymphoma development based on persistent glandular swelling, confirmed after parotid biopsy. Six patients (17%) presented with a parotid gland tumor initially; in these patients a diagnosis of MALT lymphoma in association with SS was made following the parotid biopsy.

Median age at MALT lymphoma diagnosis was 55 years (range 26–84 yrs). MALT lymphoma was localized in the parotid gland in all cases (n = 35). The majority of patients, 26 (74%) out of 35, had localized disease. Five patients (14%) had locally disseminated disease, and 4 patients (11%) had disseminated disease (bone marrow in 1 patient, lacrimal gland involvement in 2, and involvement of the stomach in 1). Seven patients had high SS disease activity initially, as exemplified by monoclonal gammopathy/cryoglobulins, increased IgM-RF, and 1 or more severe extraglandular manifestations (arthritis, vasculitis; pulmonary, hepatic, or renal SS involvement).

Treatment and response of MALT lymphoma. Ten patients (28%) received no initial treatment because the lymphoma was asymptomatic. These patients were closely monitored ("watchful waiting"; Tables 3 and 4). In 5 patients a diagnostic superficial parotidectomy was performed because of persistent symptomatic unilateral parotid gland swelling. The treatment resulted in complete excision of the lymphoma in 3. Three patients received radiotherapy, including the 2 patients with incomplete excision of the lymphoma. Thirteen patients (37%) were treated with rituximab only; 7 of those patients participated in a phase II study with rituximab[38]. Six patients (17%) were treated with R-CP.

Lymphoma response in the 25 patients treated with surgery, radiotherapy, rituximab, or R-CP was as follows: CR in 14 (56%) patients, PR in 1 patient (4%), and SD in 10 patients (40%). No serious side effects were observed.

A reduction in extraglandular manifestations (arthritis, vasculitis; pulmonary, hepatic, or renal SS involvement) was seen in all systemic-treated patients (rituximab or R-CP).

Improvement in serologic measures (increased C4, no presence of cryoglobulins and M-protein) was observed in the majority of patients (9 out of 13) treated with rituximab. Three of the 4 patients that did not show improvement in serologic measures after rituximab treatment initially had high SS disease activity. All 6 patients treated with R-CP showed normalization of these serologic measures after treatment (Table 5).

Longterm outcome and followup. After a median followup of 76 mo (range 16–153 mo) after initial diagnosis of MALT-SS, progression or recurrence of MALT lymphoma was observed in 10 out of 35 patients at a median time of 45 mo after diagnosis (range 4–98 mo; Table 6). Five of the 10 patients with progression or recurrence of lymphoma had

Table 2. SS characteristics of the MALT-SS patients.

Patient	Age†/ Sex	Year of SS Diagnosis	Year of MALT Diagnosis	Risk Factors	Extraglandular Manifestations	Anti-SSA/SSB	IgG, g/l	IgM-RF, KIU/l
1*	68 F	1997	1997	PGS, M-protein	Arthralgia, arthritis	SSB	12.6	445
2	77 F	1998	1998	—	Arthralgia, fatigue	—	16.3	860
3	61 F	1998	1998	PGS, M-protein	None	SSA	10.1	< 11
4	33 M	1992	1999	PGS	Arthritis, fatigue	SSA/SSB	22.0	107
5	55 F	1999	1999	—	Arthralgia, arthritis	SSA	16.5	95
6	28 F	1990	2001	PGS, low C4	Arthralgia, arthritis, RP	SSA/SSB	24.0	80
7	64 F	2001	2001	PGS, low C4	Arthralgia, arthritis, fatigue	SSA/SSB	10.3	NA
8*	36 F	1998	2002	PGS, purpura, low C4, M-protein, cryoglobulins	Arthralgia, fatigue, RP, vasculitis	SSA/SSB	19.6	461
9	62 M	2003	2003	—	Arthralgia, fatigue	SSA/SSB	22.1	267
10*	54 F	1990	1997	PGS, cryoglobulins	Fatigue, vasculitis, pulmonary, hepatic and renal involvement	SSA	6.8	101
11	48 F	1998	1998	PGS	None	SSA/SSB	12.4	80
12	72 F	2003	2003	PGS	Arthralgia, fatigue	SSA/SSB	14.8	98
13*	50 F	1995	2004	PGS, low C4, M-protein	Arthritis, fatigue, RP, vasculitis and esophageal involvement	SSA/SSB	5.9	342
14*	43 F	2000	2004	PGS, M-protein	Arthritis, fatigue, RP	SSA/SSB	14.7	124
15	57 F	2001	2004	PGS	Fatigue	SSA	15.0	30
16	43 F	1990	2002	—	Fatigue	SSA/SSB	25.0	107
17	76 F	2003	2003	M-protein, low C4	Arthralgia, RP	—	15.5	399
18	58 F	2004	2004	—	Fatigue	SSA	15.1	113
19	36 M	2004	2004	PGS	Fatigue	SSA/SSB	17.4	26
20	57 F	1989	2004	PGS	Fatigue	SSA/SSB	23.3	88
21	67 F	2005	2005	PGS	Fatigue, RP	SSA/SSB	17.3	136
22	51 F	2005	2005	Low C4	Arthralgia, fatigue	SSA/SSB	38.5	278
23	57 F	2000	2003	PGS, normal C4	Fatigue	SSA/B	25.9	96
24	68 F	1990	2003	PGS	Arthralgia	SSA	23.3	440
25	41 F	2005	2005	PGS	Arthralgia, fatigue	SSA/B	18.9	152
26	65 F	2000	2006	PGS	Fatigue	SSA	18	1860
27	72 F	2006	2006	PGS	Fatigue, RP	SSA	14.1	510
28*	64 F	2001	2005	PGS, low C4, M-protein, cryoglobulins	Fatigue, vasculitis, pulmonary and esophageal involvement, polyneuropathy	SSA	19.4	2370
29*	76 F	1992	2006	PGS, low C4, M-protein, cryoglobulins	Arthritis, RP	SSA	10.6	172
30	65 F	2004	2005	PGS	Arthralgia	SSA	12.4	93
31	60 F	2007	2007			—	11.2	19
32	85 F	2007	2007	PGS, low C4	Fatigue	SSA/SSB	15.0	20
33	42 F	2005	2007	PGS, low C4		—	12.9	9
34	54 F	2006	2007	PGS	Arthralgia	SSA/SSB	13	41
35	37 F	2005	2008	PGS		SSA	13.1	183

* High SS disease activity. † At time of diagnosis of MALT-SS. SS: Sjögren's syndrome; PGS: parotid gland swelling; M-protein: monoclonal protein; IgG: immunoglobulin G (normal 8.5–15 g); IgM-RF: IgM rheumatoid factor (normal < 11 KIU/l); RP: Raynaud's phenomenon; MALT: mucosa-associated lymphoid tissue.

high SS disease activity initially (Table 6). The difference in disease-free survival of patients with initial low vs high SS disease activity was significant ($p < 0.05$; Figure 1).

In the "watchful waiting" group, 2 of the 10 patients showed MALT lymphoma progression, after 34 and 81 mo. One of these patients also had high SS disease activity at the initial diagnosis of MALT. All other patients in the "watchful waiting" group had low SS disease activity.

Increased extraglandular SS activity without progression of MALT lymphoma necessitating immunosuppressive retreatment was observed in 1 patient treated with rituximab at 27 mo after MALT diagnosis (Table 6).

Transformation to high-grade lymphoma was not observed. Thirty-four patients are alive at a median followup of 76 mo (range 16–153 mo); 1 patient died of pneumonia unrelated to MALT lymphoma.

Table 3. Treatment and outcome of the 35 patients with MALT-SS.

Treatment	N	Stage	Initial High SS Disease Activity	Total	Outcome CR	PR	SD
Watchful waiting	10	L	0	9	0	0	9
		LD	1	1	0	0	1
		DD	0	0	0	0	0
Surgery	3	L	0	1	1	0	0
		LD	0	1	0	0	1
		DD	0	1	0	0	1
Radiotherapy	1	LD	1	1	0	0	1
Surgery/radiotherapy	2	L	0	1	1	0	0
		LD	0	0	0	0	0
		DD	0	1	1	0	0
Rituximab	13	L	1	11	3	1	7
		LD	2	2	2	0	0
		DD	0	0	0	0	0
R-CP	6	L	0	4	4	0	0
		LD	0	0	0	0	0
		DD	2	2	2	0	0
Total	35		7	35	14	1	20

L: localized disease; LD: locally disseminated disease; DD: disseminated disease; CR: complete remission; PR: partial response; SD: stable disease; R-CP: rituximab-cyclophosphamide-prednisone combination.

Table 4. Characteristics of MALT-SS patients regarding MALT lymphoma, treatment, and outcome.

Patient	Stage	Treatment	MALT Response After 12 Weeks	Progression/Time to Progression, mo Lymphoma	SS	Retreatment	Response	Survival/mo
1*	L	Watchful waiting	SD	Yes/81	No	Surgery	CR	Alive/153
2	L	Watchful waiting	SD	No	No			Deceased/109†
3	DD	Surgery	SD	No	No			Alive/141
4	L	Surgery	CR	Yes/85	No	R-CP	CR	Alive/124
5	L	Watchful waiting	SD	No	No			Alive/128
6	L	Surgery & radiotherapy	CR	No	No			Alive/102
7	L	Watchful waiting	SD	No	No			Alive/108
8*	LD	Rituximab	CR	No	Yes/27	CYC	Stable	Alive/91
9	L	Rituximab	SD	No	No			Alive/78
10*	LD	Radiotherapy	SD	Yes/98	Yes/98	CYC	Stable	Alive/153
11	L	Rituximab	CR	No	No			Alive/141
12	L	Rituximab	CR	No	No			Alive/75
13*	L	Rituximab	SD	Yes/4	Yes/4	Rituximab	Stable	Alive/66
14*	LD	Rituximab	CR	Yes/52	No	Rituximab	Stable	Alive/70
15	LD	Surgery	SD	Yes/73	No	Radiotherapy	CR	Alive/100
16	L	Rituximab	CR	No	No			Alive/94
17	L	Rituximab	SD	No	No			Alive/83
18	L	Rituximab	SD	No	No			Alive/64
19	L	Rituximab	SD	No	No			Alive/67
20	L	Watchful waiting	SD	No	No			Alive/64
21	L	Rituximab	PR	Yes/9	No	Rituximab	Stable	Alive/57
22	L	Rituximab	SD	No	No			Alive/58
23	DD	Surgery & radiotherapy	CR	Yes/39	No	R-CP	Stable	Alive/85
24	L	Watchful waiting	SD	No	No			Alive/75
25	LD	Watchful waiting	SD	No	No			Alive/53
26	L	R-CP	CR	No	No			Alive/49
27	L	Watchful waiting	SD	No	No			Alive/46
28*	DD	R-CP	CR	No	No			Alive/50
29*	DD	R-CP	CR	Yes/15	No	Radiotherapy	CR	Alive/47
30	L	Watchful waiting	SD	Yes/34	No	Radiotherapy	CR	Alive/50
31	L	R-CP	CR	No	No			Alive/36
32	L	R-CP	CR	No	No			Alive/28
33	L	Watchful waiting	SD	No	No			Alive/28
34	L	R-CP	CR	No	No			Alive/26
35	L	Rituximab	SD	No	No			Alive/16

* High SS disease activity. † Patient died of pneumonia unrelated to MALT lymphoma. L: localized disease; LD: locally disseminated; DD: disseminated disease; CR: complete response; SD: stable disease; PR: partial response; R-CP: rituximab with cyclophosphamide and prednisone; CYC: cyclophosphamide.

Table 5. Adverse factors before and after initial treatment of the MALT-SS patients.

Patient	Adverse Factors				Progression/Recurrence
	Serologic Indications Before Treatment	Extraglandular Manifestations Before Treatment	Serologic Indications After Treatment	Extraglandular Manifestations After Treatment	
1*	PGS, M-protein	Arthralgia, arthritis	NA	NA	MALT lymphoma
2	—	Arthralgia, fatigue	NA	NA	
3	PGS, M-protein	None	M-protein	None	
4	PGS	Arthritis, fatigue	—	Arthritis	MALT lymphoma
5	—	Arthralgia, arthritis	NA	NA	
6	PGS, low C4	Arthralgia, arthritis, RP	—	Arthralgia, arthritis, RP	
7	PGS, low C4	Arthralgia, arthritis, fatigue	NA	NA	
8*	PGS, purpura, low C4, M-protein, cryoglobulins	Arthralgia, fatigue, RP, vasculitis	Low C4, cryoglobulins	None	SS
9	—	Arthralgia, fatigue		None	
10*	PGS, low C4	Fatigue, vasculitis, pulmonary, hepatic and renal involvement	Low C4	Pulmonary, hepatic, and renal involvement	MALT lymphoma & SS
11	PGS	None	—	None	
12	PGS	Arthralgia, fatigue	—	None	
13*	PGS, low C4, M-protein	Arthritis, fatigue, RP, vasculitis, esophageal involvement	Low C4, M-protein	RP, esophageal involvement	MALT lymphoma & SS
14*	PGS, M-protein	Arthritis, fatigue, RP	M-protein	RP	MALT lymphoma
15	PGS	Fatigue	—	Fatigue	MALT lymphoma
16	—	Fatigue	—	Fatigue	
17	M-protein, low C4	Arthralgia, RP	Low C4	Arthralgia	
18	—	Fatigue	_	Fatigue	
19	PGS	Fatigue	—	None	
20	PGS	Fatigue	NA	NA	
21	PGS	Fatigue, RP	—	Fatigue, RP	MALT lymphoma
22	Low C4	Arthralgia, fatigue	—	Arthralgia	
23	PGS	Fatigue	—	Fatigue	MALT lymphoma
24	PGS	Arthralgia	NA	NA	
25	PGS	Arthralgia, fatigue	NA	NA	
26	PGS	Fatigue	—	Fatigue	
27	PGS	Fatigue, RP	NA	NA	
28*	PGS, low C4, M-protein, cryoglobulins	Fatigue, vasculitis, pulmonary and esophageal involvement, polyneuropathy	—	Polyneuropathy, pulmonary and esophageal involvement	
29*	PGS, low C4, M-protein, cryoglobulins	Arthritis, RP	_	None	MALT lymphoma
30	PGS	Arthralgia	NA	NA	MALT lymphoma
31			—	None	
32	PGS, low C4	Fatigue	—	None	
33	PGS, low C4		NA	NA	
34	PGS	Arthralgia		Arthralgia	
35	PGS			None	

* High SS disease activity. PGS: parotid gland swelling; RP: Raynaud's phenomenon; M-protein: monoclonal protein; NA: not applicable ("watchful waiting" regimen).

DISCUSSION

In our retrospective study we analyzed the clinical course of patients with SS and associated MALT lymphoma. Patients with SS who had MALT lymphoma of the parotid gland usually had localized disease. High SS disease activity at presentation (i.e., multiple extraglandular SS manifestations, low C4, presence of cryoglobulins and/or M-protein) was associated with clinical progression or recurrence of MALT lymphoma and/or deterioration of SS during followup necessitating (re)treatment. Although the median followup of 6 years is still relatively short, transformation to high-grade lymphoma was not observed and no patient died from lymphoma.

MALT lymphoma in patients with SS is part of a spec-

Table 6. Patients failing initial treatment policy, resulting in progression or recurrence of MALT lymphoma and/or SS disease activity.

Initial Treatment	N	MALT Stage	Initial SS Disease Activity	Initial Treatment Response	Progression/Recurrence	Months after Initial Diagnosis	(Re-)treatment	Response
Watchful waiting	2	L	High	SD	MALT lymphoma	81	Surgery	CR
		L	Low	SD	MALT lymphoma	34	Radiotherapy	CR
Surgery	2	L	Low	CR	MALT lymphoma	85	R-CP	CR
		LD	Low	SD	MALT lymphoma	73	Radiotherapy	CR
Radiotherapy	1	LD	High	SD	MALT lymphoma & SS disease activity	98	CYC	Stable
Surgery/radiotherapy	1	DD	Low	CR	MALT lymphoma	39	R-CP	Stable
Rituximab	4	L	High	SD	MALT lymphoma & SS disease activity	4	Rituximab	Stable
		LD	High	CR	MALT lymphoma	52	Rituximab	Stable
		LD	High	CR	SS disease activity	27	CYC	Stable
		L	Low	PR	MALT lymphoma	9	Rituximab	Stable
R-CP	1	DD	High	CR	MALT lymphoma	15	Radiotherapy	CR

CYC: cyclophosphamide; L: localized disease; LD: locally disseminated disease; DD: disseminated disease; SD: stable disease; PR: partial response; CR: complete response; R-CP: rituximab with cyclophosphamide and prednisone.

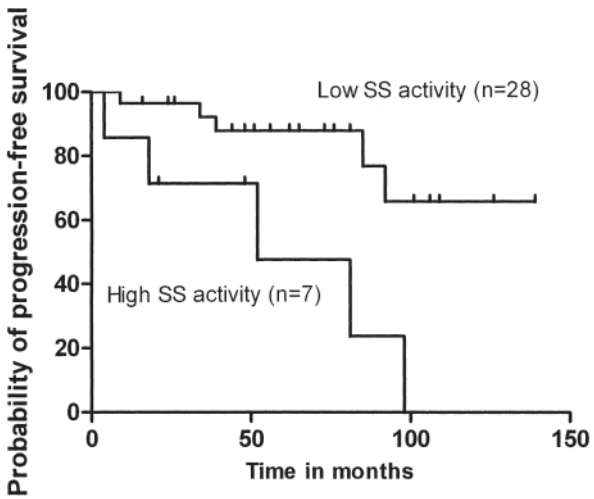

Figure 1. Progression-free survival of MALT lymphoma according to initial high or low SS disease activity.

trum ranging from indolent asymptomatic lymphoma and low SS disease activity to locally disseminated or disseminated lymphoma and severe extraglandular SS manifestations. According to the latest diagnostic consensus criteria, preexistent lymphoma is considered to be an exclusion criterion of SS, because lymphoma of the parotid gland itself can cause mouth dryness and parotid gland swelling[42]. In our opinion, however, MALT lymphoma of the salivary gland should not be considered as an exclusion criterion for the diagnosis of SS. As also shown in the study by Ekström Smedby, *et al*[6], the great majority of these lymphomas are associated with SS or other autoimmune diseases[17,55]. According to that study, vasculitis, peripheral nerve involvement, glomerulonephritis, fever, anemia, and lymphopenia are observed significantly more often in patients with MALT-SS than in the general SS population[5]. In our study the majority of patients (71%) had no severe extraglandular manifestations. This discrepancy might be explained by the inclusion of 11 patients in whom a MALT lymphoma was detected during diagnostic investigation for SS, which in our institution included a parotid biopsy instead of a labial biopsy. The parotid biopsy is preferred because of its association with less morbidity and diagnostic potential comparable to that of a labial biopsy in the diagnosis of SS[43]. Other studies have found an incidence of 3.4% to 7% of MALT lymphoma within their SS cohorts[1,2,5]. Since the parotid is the gland most commonly involved in MALT lymphoma, routine use of the parotid biopsy for diagnosis of SS likely explains a slightly higher incidence of MALT lymphoma in our SS cohort (11%)[56], as well as the higher frequency of lymphoma patients without severe extraglandular manifestations of SS.

The high survival rate in our cohort (97%; 1 patient died of pneumonia unrelated to MALT lymphoma) is in accord with reports of MALT lymphoma not associated with SS[13,14]. Progression/relapse was seen in 29% of our patients; this finding is also in accord with the 30% progression/relapse rate reported for MALT lymphoma not associated with SS[57].

The staging system for MALT-SS used in this study (see Materials and Methods) may provide better prognostic information at diagnosis than the traditional Ann Arbor staging. Although MALT lymphoma in SS can localize in other mucosal sites, it usually localizes in the main target of the autoimmune disease, i.e., the parotid gland[16,56]. It is debatable whether it is necessary to perform full staging in patients with MALT-SS, including CT scans of thorax and abdomen and bone marrow biopsy. Bone marrow involvement is rare in the patients described, and probably does not influence prognosis or treatment[12].

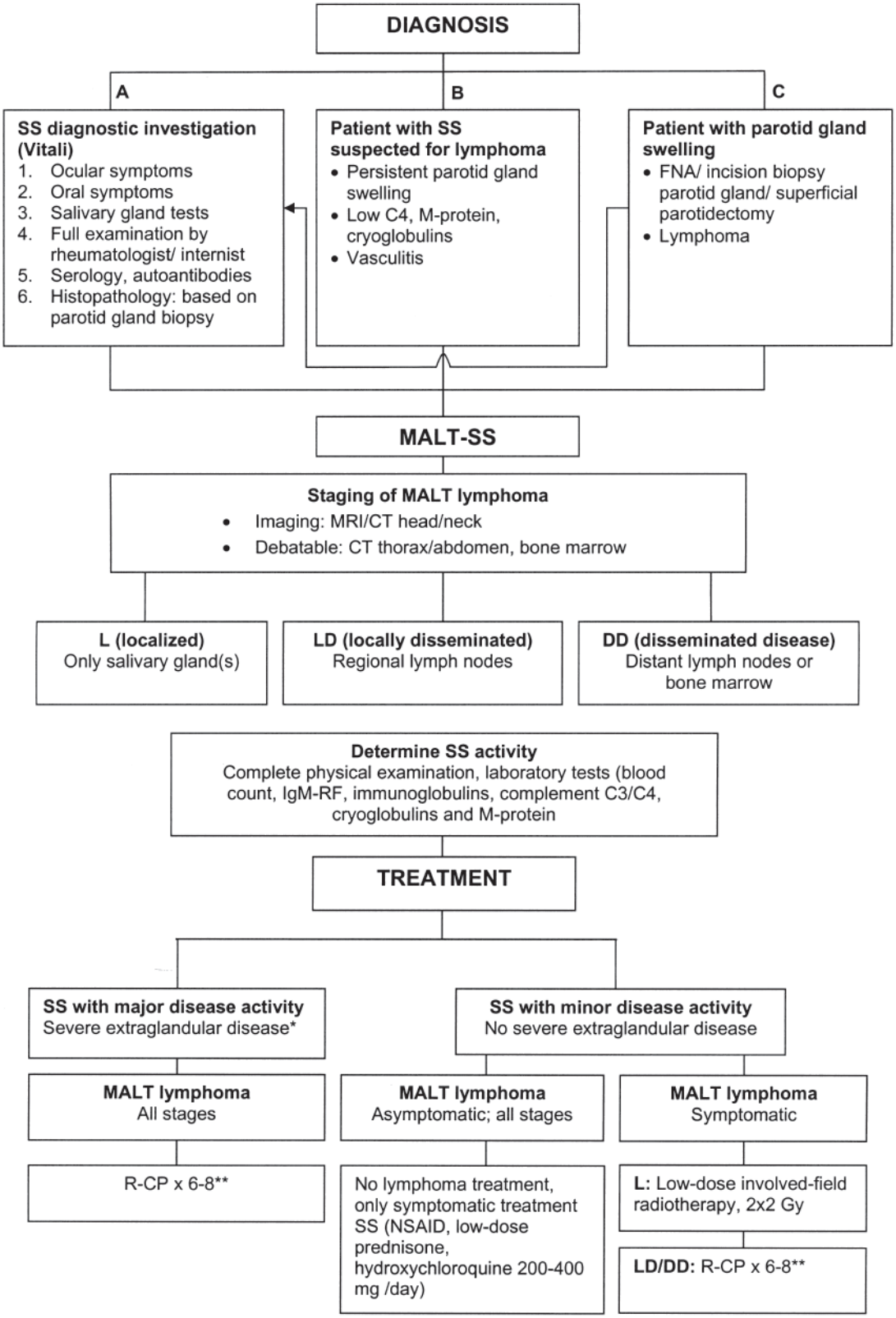

Figure 2. Management of mucosa-associated lymphoid tissue-type lymphoma of parotid gland and associated Sjögren's syndrome (MALT-SS). FNA: fine-needle aspiration; R-CP: rituximab with cyclophosphamide and prednisone; NSAID: nonsteroidal antiinflammatory drugs. * Extraglandular disease: polyarthritis/myositis, glomerulonephritis, nervous system involvement, cryoglobulinemic vasculitis, other severe organ involvement, serological abnormalities: cryoglobulinemia, C4 < 0.10 g/l. ** Six intravenous infusions of 375 mg/m^2 of rituximab and 6-8 cycles of cyclophosphamide, given every 3 weeks[59].

In some patients with locally disseminated or disseminated disease, it may be difficult to decide whether symptoms should be attributed to lymphoma activity or to SS activity. For example, weight loss might be attributed to lymphoma activity, but could also be part of SS disease activity. In these patients, both lymphoma and SS disease activity need to be addressed: not only the clinical characteristics of the lymphoma, but also the severity of SS manifestations might determine the choice of treatment. We are aware that an international standardized activity score is needed for evaluating SS disease activity. However, in the time frame within which this cohort was diagnosed, no standardized activity score was available[51,52]. At that time the disease activity was assessed by a team of experts according to our own standardized methods (as above).

As observed in this analysis, "watchful waiting" seems a suitable option in patients with asymptomatic MALT lymphoma in the absence of high SS disease activity, since most patients remained asymptomatic for a long period of time (Figure 1). In patients with symptomatic MALT lymphoma, such as a persistent disabling parotid gland swelling, but with low SS disease activity, local treatment with low-dose involved-field radiotherapy to spare remaining salivary function (2×2 or 1×4 Gy) might be sufficient. However, experience with low-dose involved-field radiotherapy in extranodal MALT lymphoma is limited.

Our study also suggests that in patients with MALT-SS with initial high SS disease activity, rituximab monotherapy might not be sufficient, because these patients required retreatment due to recurrence of MALT lymphoma and/or development of SS disease activity. Also, normalization of serological variables was not seen (low C4 levels and presence of cryoglobulins and/or M-protein). In these patients, treatment might have to include more intensive immunosuppressive therapy, for instance a combination of rituximab with cyclophosphamide and prednisone (R-CP). This combination therapy is effective in the treatment of both indolent lymphoma and autoimmune disease[58,59].

Current guidelines for management and treatment of patients with MALT-SS in our center are based on the treatment experience set out in this article (Figure 2): (1) Asymptomatic MALT and low SS disease activity: watchful waiting. (2) Symptomatic local MALT, no or low SS disease activity: radiotherapy. (3) High SS disease activity and asymptomatic MALT: rituximab only (phase II trial) or immunochemotherapy of R-CP. And (4) Symptomatic MALT and high SS disease activity: R-CP.

Although our study indicates that most treated patients fare well, recurrences may occur. It remains to be determined whether these patients might benefit from maintenance B cell depletion therapy, as in indolent B cell lymphoma and autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus.

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