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Most cases of primary salivary mucosa-associated lymphoid tissue lymphoma are associated either with Sjoegren syndrome or hepatitis C virus infection

Achille Ambrosetti,[1] Roberta Zanotti,[1] Cristian Pattaro,[2] Lorenza Lenzi,[1] Marco Chilosi,[3] Paola Caramaschi,[1] Luca Arcaini,[4] Felice Pasini,[1] Domenico Biasi,[1] Ester Orlandi,[4] Mariella D'Adda,[1] Marco Lucioni[5] and Giovanni Pizzolo[1]

Departments of [1]Clinical and Experimental Medicine, [2]Medicine and Public Health, [3]Pathology, University of Verona, Verona, [4]Division of Hematology, and [5]Department of Pathology, University of Pavia, Pavia, Italy

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Correspondence: Achille Ambrosetti MD, Divisione di Ematologia, Policlinico G.B. Rossi., Piazzale L.A. Scuro 10, 37134 Verona, Italy.
E-mail: achille.ambrosetti@univr.it

Summary

Salivary gland mucosa-associated lymphoid tissue (MALT) lymphomas (SGML) are rare, as are data concerning their behaviour. We analysed clinical features at presentation, particularly the association with Sjoegren syndrome (SS) and hepatitis C virus (HCV) infection, and outcome in 33 cases of SGML diagnosed between March 1985 and April 2003. There were five males and 28 females, with a median age of 61 years. At presentation, 12/33 (36%) had multiple salivary glands or mucosal involvement and four had bone marrow infiltration. Ann Arbor stage was IE in 15 (46%), IIE in four (12%) and IV in 14 patients (42%). Fifteen patients had a history of SS (46%), two of other autoimmune diseases, seven of HCV infection. No case had both SS and HCV. Of the 29 treated patients, 17 received surgery or local radiotherapy; 69% achieved complete remission. Histological transformation occurred in four (12%). Five patients died (three of lymphoma, two of unrelated causes). The 5 year-overall survival (OS), cause-specific survival and progression-free survival was 85 ± 8%, 94 ± 6% and 65 ± 10% respectively. Overall, the disease course was indolent, despite the advanced stage at diagnosis, and local therapy often appeared to be adequate. The only prognostic factors influencing OS were histological transformation and age. The close association of SGML with either autoimmune diseases or HCV infection in our series (73%) confirms their possible role in the pathogenesis of these lymphomas.

Keywords: mucosa-associated lymphoid tissue lymphomas, salivary glands, Sjoegren syndrome, hepatitis C virus infection, prognostic factors.

Mucosa-associated lymphoid tissue (MALT) lymphomas represent about 8% of all non-Hodgkin's lymphoma (NHL) cases and involve preferentially the gastrointestinal (GI) tract, mainly the stomach (Isaacson, 1999). Non-gastrointestinal (non-GI) MALT lymphoma may arise at different sites, such as salivary glands, respiratory tract, thyroid, ocular adnexa, breast, skin, kidney, liver, etc. (Cavalli *et al*, 2001). MALT lymphomas present frequently as localized, indolent disease, predominantly in adult patients (aged over 50 years), with female predominance (Thieblemont *et al*, 1997). They usually arise in response to infectious or autoimmune conditions, such as *Helicobacter pylori* (HP) infection in the stomach, Hashimoto thyroiditis in the thyroid gland and lymphoepithelial sialadenitis (LESA), mostly associated with the Sjoegren's syndrome (SS), in the salivary glands (Cavalli *et al*, 2001). Moreover, a high incidence of hepatitis C virus (HCV) infection (50%) has been reported in patients affected by MALT lymphoma (Luppi *et al*, 1996).

MALT lymphoma is the most frequent histotype among the primary lymphoma of salivary glands (PSGL), which represent 1·7–8·6% of all salivary gland tumours and about 1% of all NHL cases (Gleeson *et al*, 1986; Sarris *et al*, 1997; Zucca *et al*, 1999). Although salivary glands are one of the main sites involved by non-GI MALT lymphoma, salivary gland MALT lymphomas (SGML) are infrequent, and data available concerning their clinical behaviour and the best treatment are scanty (Takahashi *et al*, 1992; Balm *et al*, 1993; Shi *et al*, 2001).

We report 33 consecutive cases of primary SGML observed in our Institutions, in order to assess their clinical features at

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presentation, the association with coexisting disorders, the course of the disease and the response to therapy.

Methods

We retrospectively evaluated 33 patients affected by primary SGML consecutively observed in our Institutions between March 1985 and April 2003. The diagnosis of lymphoma was made by histological and immunohistochemical examination of salivary tissue, obtained either by surgical biopsy or complete surgical resection. Histological diagnosis was made or revised, by multiple pathological review, according to the Revised European-American Lymphoma (REAL)/World Health Organization (WHO) classifications (Harris *et al*, 1994, 2000), with the aid of immunohistochemical markers (CD20, CD5, CD21, CD10, CD3, kappa/lambda light chains), performed using standardized methods and reagents (all purchased from DakoCytomation, Glostrup, Denmark). The pattern of expression of the different antigens tested is summarized in Table I.

Cases were considered primary SGML if the salivary involvement was clinically predominant, requiring diagnostic investigation, and primary treatment (Zucca *et al*, 2003).

Staging procedure

Clinical staging at diagnosis included complete physical examination, routine laboratory (erythrocyte sedimentation rate, full blood count with differential, biochemical profile, serum protein electrophoresis), chest X-ray, neck and abdominal ultrasound, thoracic and abdominal computed tomography scan. Lactate dehydrogenase (LDH) serum levels were tested in 28/33 cases. A bone marrow biopsy was performed in 31/33 cases. Eighteen patients underwent oesophagogastroduodenoscopy (EGDS) with multiple biopsies. All patients were evaluated for the possible association with autoimmune diseases; serology for HCV was tested in 26 patients: performance status (PS) was evaluated according to the Eastern Cooperative Oncology Group (ECOG) scale. Patients were staged according to the original Ann Arbor classification (Carbone *et al*, 1971). Cases were assigned to an International Prognostic Index (IPI) risk group according to the published criteria (Shipp *et al*, 1993).

After treatment all initial disease parameters were evaluated by physical examination, imaging and/or endoscopic studies when required. Bone marrow biopsy was repeated when involved at diagnosis.

Table I. Immunohistochemical findings in 33 cases of SGML.

Antigen	CD20	CD5	CD10	CD21	CD3	Cy light chain*
Tested cases (*n*)	33	30	22	18	28	24
Positive	33 (100%)	0	0	3 (17%)	0	17 (71%)

*Restricted light chain cytoplasmic expression in plasmacell and/or lymphoplasmacytoid elements (κ+ 15 cases; λ+ 2 cases).
SGML, salivary gland mucosa-associated lymphoid tissue lymphomas.

Treatment modalities

Four patients were not treated initially. One refused treatment; in the remaining three cases a 'watch and wait' policy was decided. Primary treatment was local in 17 patients: surgical resection in 13 (followed by radiotherapy in five) and local radiotherapy alone in four cases (42–50 Gy). Chemotherapy was administered in 11 patients: alone in eight cases, after surgery in one and in combination with surgery and radiotherapy in two (in seven cases a single alkylating agent was used and four cases were treated with a cyclophosphamide, hydroxydaunomycin, oncovin, prednisone (CHOP)-like regimen). One patient with associated chronic hepatitis C received α-interferon therapy 3 million units (MU)/three times weekly for 6 months and than 5 MU/three times weekly for 11 months.

Analyses

Complete remission (CR) was defined as the complete disappearance of all clinical evidence of lymphoma. Partial response (PR) was defined as >50% regression. Stable disease (SD) was defined as a <50% decrease or <50% increase of the known sites of disease. Relapsing or progressive disease (PD) was defined as the appearance of any new lesion or increase of at least 50% in size of the previously involved sites. Overall survival (OS) was defined as the time from diagnosis to death or last follow-up. Cause-specific survival (CSS) was measured from diagnosis to the time of death from disease or treatment-related causes. Progression-free survival (PFS) was measured from the date of first line treatment, or of diagnosis in untreated patients, to the date of first progression or last follow-up.

The patient characteristics at diagnosis that were analysed to determine any influence on survival were: sex, age, stage, PS, B symptoms, IPI, multiple involvement of salivary glands or other multiple mucosal sites, lymph nodes and bone marrow involvement, Hb levels, LDH serum levels, associated diseases (autoimmune disease and HCV infection). We also evaluated the impact on the outcomes of the type of treatment, the achievement of CR and the histological transformation in high-grade lymphoma.

Overall survival, CSS, and PFS curves were estimated according to Kaplan–Meier method. The associations with prognostic factors were tested using the log-rank test. Multivariate analysis was not performed because of the low number of events.

Results

Patients characteristics

Pretreatment characteristics of the 33 patients are summarized in Table II.

Median age at diagnosis was 61 years (range 21–81). There were five males and 28 females (ratio 0·2). In all patients the presenting symptom was a solid, indolent mass. Ann Arbor stage was IE in 15 (46%), IIE in four (12%) and IV in 14 (42%). The primary sites involved by the lymphoma are detailed in Table III. The majority of patients (64%) had single salivary gland involvement, mainly of the parotid (52%).

Table II. Pretreatment characteristics of the 33 patients with SGML.

Features	No. of patients (%)
Age (years)	
<60	16 (48)
≥60	17 (52)
Sex	
Male	5 (15)
Female	28 (85)
Performance status (ECOG)	
0–1	32 (97)
≥2	1 (3)
Ann Arbor Stage	
IE	15 (46)
IIE	4 (12)
IV	14 (42)
B symptoms	
Absent	32 (97)
Present	1 (3)
Single salivary gland involvement	21 (64)
Multiple salivary glands or multiple MALT involvement	12 (36)
Bone marrow involvement	
Absent	27 (82)
Present	4 (12)
Unknown	2 (6)
Nodal involvement	
Absent	24 (73)
Present	9 (27)
Hb ≥ 12 g/dl	24 (73)
Hb < 12 g/dl	9 (27)
Serum LDH levels	
Normal	24 (73)
Increased	4 (12)
Unknown	5 (15)
International Prognostic Index	
Low to low/intermediate risk	19 (58)
Intermediate/high to high risk	9 (27)
Unknown	5 (15)
HCV serology	
Positive	7 (21)
Negative	19 (58)
Unknown	7 (21)
Associated autoimmune disease	
Sjogren syndrome	15 (46)
Scleroderma	1 (3)
Rheumatoid arthritis	1 (3)

SGML, salivary gland mucosa-associated lymphoid tissue (MALT) lymphomas; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; HCV, hepatitis C virus.

Lymph nodes involvement was present at diagnosis in nine patients (locoregional in seven, mediastinal and/or abdominal in two). EGDS, performed in 18 patients, demonstrated lymphomatous infiltration of the stomach, with MALT histology, in one case (HP-negative).

Fifteen patients had a history of SS, one of scleroderma and one of rheumatoid arthritis. Of the 26 patients tested, seven were HCV antibody (Ab) positive and six were diagnosed with a chronic hepatitis; none of the autoimmune disease patients tested for HCV serology (14/17) was HCV-Ab positive.

A serum monoclonal component (IgG or IgM) was documented in eight cases (25%). In 11/15 (73%) tested cases cryoglobulinaemia was detectable. Of these 11 patients with cryoglobulinaemia, five were HCV-Ab positive and six were affected by SS.

Treatment

One of the four patients who did not receive initial treatment progressed locally after 82 months, three remained stable with follow-up durations of 86, 6 and 5 months.

After first-line therapy, 20 of the 29 treated patients achieved a CR (69%), seven a PR (24%), one did not respond and one is not yet evaluable. Among patients with stage I–II, CR was obtained in 13/14 cases (93%) receiving local treatment alone (surgery and/or radiotherapy) and in 2/2 treated also with additional chemotherapy. Of the remaining stage I–II patients, one received chemotherapy only and achieved a PR, two were not treated. Three of the seven evaluable stage-IV patients treated with chemotherapy achieved a CR, three a PR and one did not respond. Two were not treated and three had only surgical excision. The patient treated at diagnosis with α-interferon obtained a PR; at the end of treatment HCV-RNA was still positive.

Twelve patients (36%) experienced relapsing or PD after 6–90 months (median 24). In two cases it occurred at the original sites, in three at the controlateral parotid; one patient with involvement of minor salivary glands relapsed in the right

Table III. Initial mucosal sites involved in 33 cases of SGML.

	Patients, *n* (%)
One salivary gland involvement	21 (64)
Parotid	17 (52)
Submandibular	2 (6)
Minor salivary glands	2 (6)
Multiple salivary glands or multiple MALT involvement	12 (36)
Parotid bilateral	4 (12)
Parotid + submandibular	5 (15)
Parotid + minor salivary glands	1 (3)
Parotid bil + submandibular bil + stomach	1 (3)
Parotid + lacrimal gland	1 (3)

SGML, salivary gland mucosa-associated lymphoid tissue (MALT) lymphomas.

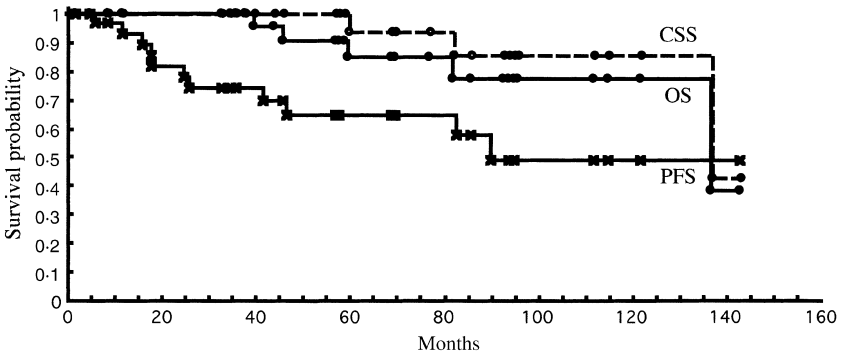

Fig 1. Overall survival (OS), cause-specific survival (CSS) and progression-free survival (PFS) of 33 patients with salivary gland mucosa-associated lymphoid tissue lymphomas.

parotid and skin, one in the lung, one in the stomach and four in the lymph nodes (locoregional in three and abdominal in one).

Histological transformation to large B-cell lymphoma occurred in 4/33 (12%) patients at 35, 57, 67 and 110 months from diagnosis. In one case this represented the first sign of disease progression.

Survival

The median duration of follow-up was 59 months (range 5–143). At the time of follow-up, 28 (85%) patients were alive, three had died of disease progression (60, 82 and 137 months from diagnosis), and two of unrelated causes. All of the patients that died of disease progression showed histological transformation.

The estimated 5-year OS, CSS and PFS of all patients was 85 ± 8%, 94 ± 6% and 65 ± 10% respectively (Fig 1).

Analysis of prognostic factors

When univariate analysis was performed age >60 years was associated with poorer OS ($P = 0{\cdot}02$), but not CSS ($P = 0{\cdot}09$) and PFS ($P = 0{\cdot}24$).

The 5-year OS for the nine patients with lymphnodal involvement at diagnosis was 50 ± 25% vs. 94 ± 5% for the remaining patients. This difference was not statistically significant ($P = 0{\cdot}06$). CSS and PFS were not influenced by lymphnodal involvement ($P = 0{\cdot}12$ and $0{\cdot}54$ respectively).

Increased serum LDH levels were associated with a poorer 5-year PFS (37 ± 28% vs. 78 ± 10% of the patients with normal LDH; $P = 0{\cdot}01$). Serum LDH levels did not influence either OS or CSS.

Gender, Ann Arbor stage IV, impaired PS, bone marrow involvement, multiple involvement of salivary glands or of multiple MALT organs, intermediate/high risk IPI, anaemia, HCV infection or autoimmune disease were not associated with poorer survival.

Overall survival and CSS were not influenced by the achievement of CR. OS, CSS and PFS rate did not differ according to the type of first-line therapy (local or systemic).

Overall survival was significantly affected by histological transformation to high-grade lymphoma: the 5-year and 10-year OS of the four patients who experienced histological transformation were 66 ± 33% and 33 ± 27% respectively, and was significantly lower than those of the 29 remaining patients (88 ± 8% at 5 and 10 years, $P = 0.04$). The relative risk of death was 7·84 (95% confidence interval: 1·31–47·0).

The only two variables significantly associated with the occurrence of histological transformation into high-grade lymphomas were age >60 years ($P = 0{\cdot}04$) and lymphnodal involvement at presentation ($P = 0{\cdot}007$). In particular, in the nine cases with nodal involvement the probability of histological transformation was 43% at 5 years vs. 7% for the remaining patients.

Discussion

Primary salivary glands lymphoma is an infrequent neoplasm that usually occurs in the parotid glands. According to the REAL/WHO classification, most of these lymphomas are classifiable as marginal-zone B-cell lymphoma, extranodal, MALT type. Our series of 33 patients with SGML is one of the largest reported to date. Published series described seven to 32 cases of SGML, and some of them are pathological studies (Takahashi *et al*, 1992; Balm *et al*, 1993; Thieblemont *et al*, 1997; Zinzani *et al*, 1999; Shi *et al*, 2001; Tsang *et al*, 2001; Wenzel *et al*, 2003). The largest report of non-GI MALT lymphomas (180 cases) recently published by Zucca *et al* (2003), and collected from various centres, included 46 SMGL, but clinical data concerning lymphomas arising in the salivary glands are limited.

In the majority of our patients with SGML (24/33–73%) the lymphoma was associated with either SS (15 cases) or other autoimmune disease (one rheumatoid arthritis and one scleroderma) or HCV infection (seven cases); in no case did the autoimmune disease coexist with HCV infection. Four of the remaining nine patients were not tested for HCV serology.

The association of PSGL with SS and LESA has been extensively reported. Approximately 20% of PSGL are associated with SS or LESA (Barnes *et al*, 1998; Harris, 1999). SS/LESA patients have a 44-fold increased risk of developing salivary or extrasalivary lymphoma, 48–75% of which are of marginal zone/MALT type (Kassan *et al*, 1978; Royer *et al*, 1997; Harris, 1999; Voulgarelis *et al*, 1999). In salivary gland

biopsies revealing LESA-like lesions, various studies found that between 25% and 80% had morphological and/or immunophenotypical evidence of low-grade MALT lymphoma (Hyjek *et al*, 1988; Takahashi *et al*, 1992; Harris, 1999).

Our study confirms the association of SGML with SS, but with a higher rate (46%) when compared with others reports of SGML or PSGL (Takahashi *et al*, 1992; Balm *et al*, 1993; Barnes *et al*, 1998). However, a significant association between SS and SGML was also recently reported by Zucca *et al* (2003).

In our series, 29% of the patients with SGML had positive serology for HCV (seven of 24 tested patients). The reported HCV seroprevalence rate in northern Italy adult general population is 3·3–3·5% (Campello *et al*, 2002; Mazzeo *et al*, 2003). An association between HCV infection and B-cell lymphoma has been largely demonstrated in several geographical areas, with a rate ranging between 7·4% and 37% (Zuckerman & Zuckerman, 2002). Among the non-GI MALT lymphomas, an association with HCV infection was recently reported for MALT lymphoma localized in the parotid gland (Zucca *et al*, 2003). HCV RNA and HCV-related antigens have been detected in the epithelial cells of salivary glands of HCV-positive patients and in residual epithelial structures in a NHL of the parotid (De Vita *et al*, 1995; Arrieta *et al*, 2001). The chronic sialadenitis, characteristic of SS and demonstrated in many HCV-infected patients (Haddad *et al*, 1992; Scott *et al*, 1997), could represent a first 'stimulus' in the aetiopathogenesis of SGML.

Lymphomas complicating SS share a number of features with lymphomas complicating HCV infection (Ferri *et al*, 1994; Zuckerman & Zuckerman, 2002): mucosal localization, marginal zone histologic subtype, associated cryoglobulinaemia. In both diseases it has been hypothesized that the first event of lymphomagenesis could be a chronic stimulation, at the site of the disease, of polyclonal B-cells secreting rheumatoid factor (RF), from which a monoclonal population could arise (Mariette, 1999). The next step would be the acquisition of chromosomal abnormalities leading to transformation into MALT lymphoma (Cavalli *et al*, 2001; Streubel *et al*, 2003). A last event (e.g. mutation of p53) could transform this low grade B-cell lymphoma into a high-grade large B-cell lymphoma (Du & Isaacson, 2002).

The median age of our patients (61 years) was similar to that reported in other series of non-GI MALT lymphoma (Thieblemont *et al*, 1997; Zinzani *et al*, 1999; Zucca *et al*, 2003) and SGML (Balm *et al*, 1993; Shi *et al*, 2001).

A prevalence of female patients was reported in the majority of non-GI MALT lymphoma series (Thieblemont *et al*, 1997; Zinzani *et al*, 1999; Liao *et al*, 2000; Sancho *et al*, 2000; Zucca *et al*, 2003), although our male/female ratio of 0·2 appears quite lower.

The percentage of Ann Arbor stage IV in our series (42%), mainly depending on the involvement of other salivary glands or MALT organs (10/14), was comparable with that reported by other non-GI MALT lymphomas series (Thieblemont *et al*, 1997; Zinzani *et al*, 1999) (34% and 37% respectively), and higher than that reported by Zucca *et al* (2003) (27%). Bone marrow infiltration was present in 12% of our patients, similarly to that reported in these series.

Both GI and non-GI MALT lymphomas are known to have an indolent natural course, irrespective of multiorgan involvement at diagnosis, and a favourable outcome. This is confirmed by our study. The 5-year OS and CSS rates of 85 ± 8% and 94 ± 6% respectively, are comparable with those reported in other series of non-GI MALT lymphomas (Thieblemont *et al*, 1997; Zinzani *et al*, 1999; Liao *et al*, 2000; Sancho *et al*, 2000; Zucca *et al*, 2003), despite the high percentage of advanced stage (IV) patients in our series.

The PFS rate was 65 ± 10%, similar to that reported by Zucca *et al* (2003) for SGML (67%).

Generally MALT lymphomas tend to diffuse to other sites within the organ of origin or to other MALT-containing organs (Isaacson, 1995; Thieblemont *et al*, 2000). In addition in our series relapse or progression occurred locally, i.e. in salivary glands or locoregional nodes, in the majority of cases (9/12 cases; 75%). The prognosis did not seem to be influenced by the spreading to other MALT organs. The adverse influence on OS of the lymphnodal involvement was not statistically significant in our series, probably because of the limited number of patients ($P = 0{\cdot}06$). However, lymphnodal involvement appeared to represent an adverse prognostic factor for non-GI MALT lymphomas in the recent report by Zucca *et al* (2003).

Transformation to high-grade lymphoma was observed in 12% (4/33) of our patients and represented a late event (median 62 months after diagnosis). This rate of transformation is similar to that reported in non-GI MALT lymphomas by Thieblemont *et al* (1997) (19%) and higher than those reported by Zucca *et al* (2003) (3%), Zinzani *et al* (1999) (0%) and Wenzel *et al* (2003) (3%), probably because of different follow-up.

In our series all disease-related deaths occurred in patients who underwent histological transformation to high-grade lymphoma: this event significantly influenced the OS. Histological transformation was significantly influenced by age and lymphnodal involvement at presentation. Dissemination to the lymph nodes could correspond to tumour progression and precede transformation to high-grade lymphoma.

The optimal therapeutic strategy in SGML has not yet been clearly defined. Our patients were treated by various means, the majority of them (59%) having received surgery and/or radiotherapy. In our series no significant differences in OS, CSS and PFS were found according to local or systemic treatment modalities, in agreement with Thieblemont *et al* (1997). The higher CR rate obtained with local therapy in the initial stages did not correspond to a better outcome. Aggressive therapy does not seem to be indicated in most cases of SGML, with the possible exception of those with lymphnodal involvement. A recent report indicated a significant activity and safety of immunotherapy with Rituximab in

MALT lymphomas (Conconi *et al*, 2003), suggesting a possible role of this kind of therapy also in SGML.

In conclusion, our series of SGML, which can be considered one of the largest published to date, confirms that SGML preferentially occur in elderly women and have an indolent course regardless of treatment type, in spite of the high percentage of advanced stages. Similarly to other non-GI MALT lymphoma, SGML diffuse preferentially to various mucosal sites, but this does not seem to influence outcome. Histological transformation and age appear the only adverse prognostic factors for OS.

Among the non-GI MALT lymphomas, SGML are characterized by a close association with SS (or other autoimmune disease) or HCV infection. This association, already reported by Zucca *et al* (2003), was strengthened by our study. Autoimmune diseases and HCV infection appeared mutually exclusive and were present in the majority (73%) of our patients, thus confirming the pathogenetic link between MALT lymphomas and chronic infections or autoimmune diseases.

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