Lymphoproliferative Disorders Associated with Sjögren Syndrome

26

Corrado Tarella, Safaa Ramadan, Angela Gueli, Simona Sammassimo, and Stefano Pileri

Sjögren syndrome (SS) is one of the most common chronic, slowly progressing systemic autoimmune diseases. It occurs in 0.1–3.0 % of the general population with a prevalence of 0.2–1.4 %. Therefore, it is the second most prevalent autoimmune disease after rheumatoid arthritis. The disease predominantly affects women with female-to-male ratio of 9:1. It develops mainly between the fourth and sixth decades of life [1–5]. Exocrinopathy with keratoconjunctivitis sicca and xerostomia are the hallmarks of the disease. However, the diversity of the clinical spectrum and disease complications is broad, and approximately half of the patients develop systemic disorders during their disease course [1–4, 6]. SS is referred to as "primary SS" if it is not associated with other autoimmune diseases; otherwise it is indicated as a secondary disease. Most of the work reviewed in this chapter refers to the primary form unless otherwise specified.

26.1 Lymphoproliferative Disorders and Sjögren Syndrome

A broad spectrum of lymphoproliferative activity has been recognized in patients with Sjögren syndrome (SS patients) over the past decades. This spectrum ranges from benign to malignant lymphoproliferation [6–14]. A series of case reports and studies demonstrated increased levels of circulating monoclonal immunoglobulins and free light chains, circulating CD5-positive B cells, and mixed monoclonal cryoglobulinemia and more importantly a high incidence of malignant non-Hodgkin lymphoma (NHL) [6, 8, 15–18]. There is considerable evidence that Sjögren syndrome carries a greater risk of developing NHL compared with other autoimmune

C. Tarella (✉) • S. Ramadan • A. Gueli • S. Sammassimo • S. Pileri
Haemato-Oncology Division, Istituto Europeo di Oncologia, European Institute of Oncology, Via Ripamonti, 435, Milan 20141, Italy
e-mail: corrado.tarella@ieo.it

D. Roccatello, L. Emmi (eds.), *Connective Tissue Disease: A Comprehensive Guide-Volume 1*, Rare Diseases of the Immune System 5,
DOI 10.1007/978-3-319-24535-5_26

diseases [6, 10–14, 19–21]. Moreover, NHL has a detrimental effect on the survival of SS patients [6, 10–14, 19, 20].

26.2 Lymphoma and Sjögren Syndrome

The association between lymphoma and autoimmunity has been known for several decades [19–22]. The first report of lymphoma in patients with Sjögren syndrome was in 1963 [15]. Thereafter, a number of case reports and studies raised concerns about the risk of lymphoma as a major complication in Sjögren syndrome [6, 18–21].

Smedby et al. conducted a population-based, case-control study in Denmark and Sweden which included 3,055 NHL patients and 3,187 matched controls who were interviewed about their history of autoimmune and chronic inflammatory disorders, markers of severity, and treatment. The overall risk (OR) for NHL was high in Sjögren syndrome, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and celiac disease. SS patients had a sixfold increased risk of NHL, which is the highest among the four autoimmune diseases (OR was 6.1, 1.5, 4.6, and 2.1, respectively) [23].

Subsequently, a meta-analysis of five studies conducted between 1987 and 2000 showed that SS patients had an 18.8 times increased risk of developing NHL compared to the general population. Similarly, NHL risk in SS patients was higher than in RA and SLE patients with a standardized incidence ratio (SIR) of 3.9 and 7.4, respectively [23].

26.3 The Incidence of Non-Hodgkin Lymphoma in Patients with Sjögren Syndrome

The exact incidence of NHL in SS patients is not well defined and has been variably reported over the years. This is largely due to disparity in the included number of patients and in the duration of follow-up in each series. The main studies are summarized in the following sections (Table 26.1).

Five main studies reported a very high risk of NHL in SS patients with an SIR ranging between 33 and 44. In an early work by the National Institutes of Health (NIH), 7 out of 136 female SS patients developed NHL 6 months to 13 years after being seen at the NIH. Compared to women in the same age range in the general population at that time, women with SS had a 43.8 times higher incidence than expected [24]. Similarly, in an Italian series of 331 SS patients, 9 were diagnosed with NHL with a relative risk (RR) of 33.3. The incidence rate of NHL was also relatively variable, 5.4/1,000 per year in the north and 4.8/1,000 per year in the center-south of the country [8].

In the third study, Davidson et al. identified 3 NHL cases among 100 SS patients within 10 years of follow-up. Considering the whole cohort, the relative risk of NHL was 14.4. SS patients express autoantibodies targeting the Ro and La

Table 26.1 Studies on the risk of non-Hodgkin lymphoma (NHL) in patients with Sjögren syndrome

Reference	No. of SS patients	No. of observed lymphomas	SIR (95 % CI)
Kassan et al. [24]	142	7	44.4 (16.7–118.4)
Kauppi et al. [30]	676	11	8.7 (4.3–15.5)
Valesini et al. [8]	295	9	33.3 (17.3–64.0)
Davidson et al. [25]	100	3	14.4 (4.7–44.7)
Pertovaara et al. [28]	110	13	13 (2.7–3.8.0)
Lazarus et al. [26]	112	11	37.5 (20.7–67.6)
Theander et al. [29]	286	11 + 1	15.57 (777–2785)
Zhang et al. [27]	1,320	8	48.1 (20.7–94.8)
Weng et al. [3]	6,911	23	7.1 (425–103)
Johnsen et al. [31]	443	7	9.0 (71–253)
Fallah et al. [32]	14,570	143	4.9 (42–58)

components of a ribonucleoprotein. These antibodies are involved in the systemic inflammation of the disease [25]. In this study, NHL occurred only in the Ro/La-seropositive patients. Therefore, by restricting the analysis to this subgroup of patients, the RR was 49.7, comparable to the level of risk indicated by Kassan et al. [24, 25]. Likewise, a significant increase in lymphoma incidence (SIR 37.5) was estimated among 112 patients with SS treated at the University College Hospital, London [26]. The fifth study retrospectively assessed malignancy risk in 1,320 SS Chinese patients. With an average follow-up of 4.4 years, patients were found to be at higher risk of malignancy compared to the general population. The SIRs for all malignancies and for lymphomas were 3.25 and 48.1, respectively [27].

In two other SS series, higher incidences of NHL in SS patients compared to the corresponding matched general population were observed (SIR = 13 and 15.57, respectively) [28, 29]. In the Finish series, 3 NHL (2 B-cell and 1 T-cell lymphoma) cases occurred compared to 0.23 expected among 110 SS patients within 2, 4, and 10 years from SS diagnosis [28], while the follow-up period was of about 7 years in the Swedish series during which 11 NHL cases were observed compared to 0.71 expected [29].

On the other hand, and compared to the previously mentioned risk rates, four studies indicated a lower NHL risk rate in SS (SIR range: 4–9), which was still significant compared to the general population. For example, the SIR for NHL was 8.7 and 4.5 in a cohort of 676 primary SS patients and 709 secondary SS patients collected from the Finnish hospitals' national discharge registry, respectively [30]. In accordance, 7 of 443 Norwegian SS patients were found to have NHL with an estimated SIR of 9.0. NHL occurred at a median time of 9.3 years (range: 6.8–18.2 years) after the diagnosis of SS [31].

In the third study, Weng et al. analyzed the SIR of NHL among 6,911 Taiwanese women affected by SS. Twenty-three patients were documented with NHL resulting in an SIR of 7.1 [3]. More recently, Fallah et al. observed 143 NHL cases after an average 9 years of follow-up of 4,570 SS patients with an SIR of 4.9 [32].

The results of the main studies addressing the relative risk of NHL occurrence in SS are summarized in Table 26.1.

26.4 Predictive Factors for the Development of Non-Hodgkin Lymphoma

Several clinical and laboratory factors are thought to be correlated with an increased risk of NHL in SS patients.

Clinical factors are mainly related to the duration and severity of the disease. This may reflect chronic antigenic stimulation, a mechanism thought to be involved in the pathogenesis of lymphoma development. These factors include prolonged parotid gland enlargement, lymphadenopathy [33, 34], vasculitis such as purpura [29, 33, 34], and inflammatory neuropathy [28]. The onset of SS at a young age has also been linked to greater NHL risk [35, 36]. In a series of 387 Italian SS patients, Baldini et al. found that salivary gland enlargement and disease duration are independent risk factors [21, 37]. This is supported by the results of a recent study by Solans-Laqué et al. who showed that the cumulative risk of developing lymphoma increased from 3.4 % in the first 5 years to 9.8 % at 15 years [38].

In another retrospective study involving 536 SS patients, the presence of neutropenia, cryoglobulinemia, splenomegaly, lymphadenopathy, and low C4 levels at diagnosis predicted a fivefold increased risk of marginal zone (MZ) lymphomas compared to patients with no risk factors, whereas lymphocytopenia was a risk factor for diffuse large B-cell (DLBC) lymphoma [39].

Theander et al. also showed that low CD4+ (hazard ratio, HR = 8.14) and a low CD4+/CD8+ ratio (HR = 10.92) are strong predictors of being diagnosed with lymphoma [29].

Other laboratory biomarkers that are considered to be risk factors for NHL include mixed monoclonal (type II) cryoglobulinemia, low serum complement (C4) levels, and the presence of monoclonal gammopathy in the serum or free light chains in the urine [22, 28, 34, 40–43]. Solans-Laqué et al. found that only hypocomplementemia and lymphocytopenia are independent risk factors. Moreover, hypocomplementemia was correlated to higher mortality [38].

Other more recently identified biologic markers are the presence of germinal center-like (GC-like) structures [44] and the focus score of lymphocytic infiltration of the minor salivary glands of SS patients. The latter is determined by the number of lymphocyte foci per 4 mm^2 of glandular tissue [45].

Theander et al. examined 175 minor salivary gland biopsies performed at baseline in SS patients. GC-like structures were significantly more frequent in patients who later developed NHL versus those without subsequent NHL (86 % versus 22 %, respectively). It is worth noting that the GC-like structures are detectable more than 7 years before lymphoma occurs [44]. However, they are not part of the routine assessment of SS patients. Therefore, measuring the focus score (high ≥ 3) could be an alternative biomarker for identifying patients at NHL risk [45].

26.5 Subtypes of Sjögren Syndrome-Associated Non-Hodgkin Lymphomas

A remarkable association between mucosa-associated lymphoid tissue (MALT) lymphomas and Sjögren syndrome is well recognized [31, 32, 40, 46, 47]. Conversely, in more recent studies, DLBC lymphoma was either as frequent as MALT or actually the most frequent subtype [29, 32, 48, 49].

Voulgarelis et al. described 33 cases of NHL in 765 SS patients. SS and NHL were diagnosed at the same time in 2 patients and in 31 others at intervals ranging from 1 to 36 years after diagnosis. Twenty-three patients (69.7 %) had low-grade lymphomas, of which 12 were MALT, 8 were small lymphocytic/plasmacytoid, 1 was small lymphocytic, 1 was monocytoid B cell, and 1 was follicular mixed large and small cell. Ten patients had intermediate- or high-grade lymphomas. Among them, three had MALT, five had large-cell immunoblastic, one had DLBC, and one had follicular lymphoma subtypes. Median survival of patients in the high/intermediate and low histological grades was 1.83 years and 6.33 years, respectively [40].

In a population-based study by Smedby et al., 12 cases of NHL occurred over a range of 2–30 years after SS diagnosis. There was a significant increase in the risk of MZ (RR = 28) and DLBC lymphomas (RR = 11) [47].

Six of the seven SS-associated lymphomas in the Norwegian series were of the MALT type. Johnsen et al. reported that among them, four were located in the parotid gland and the others in the labial salivary glands, the thymus gland, and the lingual tonsil. The seventh presented with concomitant B-cell chronic lymphocytic leukemia (B-CLL) and extranodal marginal zone (ENMZ) lymphomas [29]. Similarly, Lazarus et al. found that 8 of the 11 patients with SS-associated NHL were MALT type, 1 was high-grade NHL, and 2 were of unknown subtype [26].

More recently, Papageorgiou et al. evaluated the medical records of all consecutive patients with an initial diagnosis of primary SS at the University of Athens between 1993 and September 2013. Of the 77 patients diagnosed with NHL, MALT lymphoma constituted the majority (51/77, 66.2 %) of NHL subtypes, followed DLBC (12/77, 15.6 %) and nodal marginal zone (NMZ) lymphomas (8/77, 10.4 %). Compared to patients with DLBC, MALT lymphoma patients were significantly younger (median age was 55 versus 69 years, respectively) and developed lymphoma much earlier (median time from SS diagnosis to MALT development was 65.80 versus 97.54 months, respectively) [50].

In contrast to the above data, six other studies suggested that the incidence of SS-associated diffuse large B-cell NHL is higher than previously estimated [27, 29, 32, 48, 49, 51]. Tonami et al. reviewed 27 reported lymphoma cases in 463 patients with Sjögren syndrome. The calculated prevalence of lymphoma in patients with Sjögren syndrome was 5.8 %. Twenty-six were NHL and one was Hodgkin disease. Of the 26, only 6 were MALT, while the others were diffuse medium ($n = 10$) and diffuse large [49].

In the second study, Vasaitis et al. examined 70 SS-associated lymphomas occurring at a mean follow-up time of 13 years (3–35 years) in 236 SS patients whose data were retrieved from the national Swedish patient registry. The percentage of

MALT ($n=24$) and DLBC ($n=22$) lymphomas was quite similar (34.3 % versus 31.4 %, respectively). Involvement of the parotid gland was common among the MALT ($n=18/24$; 75 %), but not among the DLBC lymphomas ($n=2/22$; 9 %). There were only a few cases of other lymphoma subtypes: follicular mixed type and angioimmunoblastic T cell (two cases each) and follicular medium and T cell-rich B-cell type (one case each) [48].

Theander et al. also revised 12 SS-associated lymphomas, and diffuse large B cell was the most frequent subtype (7/12; 58 %), while the other 5 were small lymphocytic lymphomas ($n=3$) and follicular and anaplastic large T-cell NHL (1 case each) [29].

Fallah et al. confirmed this observation in his recent Swedish series of 143 SS-associated lymphomas. Diffuse large B-cell lymphoma was the main histological subtype ($n=41$ cases), followed by follicular cell ($n=28$), mantle cell ($n=4$), and T-cell and small lymphocytic lymphomas (one each). In addition, this cohort included 15 other unspecified NHL subtypes [32].

Voulgarelis and colleagues evaluated 584 SS patients who were diagnosed between 1980 and 2010, of whom 53 subsequently presented NHL, the majority of which were MALT (59 %) lymphomas. Nodal marginal zone lymphoma and DLBC lymphoma made up 15 % each. The remaining 11 % ($n=6$) were lymphoplasmacytic NHL ($n=2$) and small lymphocytic NHL, follicular NHL, peripheral T-cell NHL unspecified, and classic Hodgkin disease (one case each) [51].

In the Chinese cohort, seven of the eight SS-associated NHL patients had B-cell NHL and only one had T-cell NHL. Four B-cell NHLs were confirmed by parotid biopsy.

A similar number of pathologic subtypes of B-cell type, including diffuse large B-cell lymphoma and lymphomas of mucosa-associated lymphoid tissue (two cases each), one intravascular large B-cell lymphoma, and two B-cell lymphomas, unclassifiable, were seen [27].

26.6 Pathologic Features and Underlying Mechanisms

Any type of malignant lymphoma can affect the salivary glands, either primarily or secondarily [52, 53]. A further distinction should be made between tumors involving the gland parenchyma and those affecting the lymph nodes comprised within it, the latter being at times erroneously considered primary events. Herein, only “de novo” lymphoid tumors of the salivary glands will be discussed. These are indeed rare (about 7 % of all lymphomas of the head and neck) and more frequently affect the parotid gland (78 %) [54, 55]. The histotype can vary from follicular lymphoma [56] to Hodgkin lymphoma [57], although ENMZ/MALT lymphoma represents the most common variety [58, 59], thus warranting a detailed description also in the light of its shared association with SS and hepatitis C virus (HCV) infection [7, 58, 59].

From a morphologic point of view [58], ENMZ lymphoma consists of small- to medium-sized cells that display variable profiles. They may resemble centrocytes with cleaved nuclei, monocytoid B cells with a wide rim of clear cytoplasm and

distinct borders, or more rarely, small mature lymphocytes. The number of mitotic figures is usually low. Features of plasma cell differentiation are commonly seen, at times becoming prominent. Some blasts are always scattered throughout: they do not affect the clinical behavior unless they form either clusters consisting of at least 20 elements or sheetlike proliferations which are regarded as indicative of transformation into a DLBC lymphoma. Such population most often develops around reactive secondary follicles in a marginal zone distribution. Importantly, the follicles can be colonized by neoplastic cells. In the most common situation, tumoral elements overrun the lymphoid follicles, leaving behind scattered germinal center cell fragments and dispersed mantle zone cells resulting in a vague nodular pattern. At times, they may selectively infiltrate, replace, and expand germinal centers, resulting in an appearance that mimics follicular lymphoma.

An important diagnostic feature of MALT lymphomas is usually the presence of lymphoepithelial lesions, defined by the infiltration and distortion of epithelial structures by aggregates of (usually three or more) neoplastic cells [58]. This is not the case in the setting of the salivary glands. In fact, the tumor generally develops on a background of a myoepithelial sialadenitis/benign lymphoepithelial lesion [58]. When fully developed, the latter comprises atrophic acinar tissue infiltrated by small lymphocytes and plasma cells, often with reactive lymphoid follicles and characteristically with numerous epimyoepithelial islands. The first morphologic manifestation of ENMZ lymphoma is the presence of halos or collars of neoplastic cells around the epimyoepithelial islands. Such infiltrates usually show immunoglobulin light chain restriction and clonal IgVH rearrangement by polymerase chain reaction (PCR) (see below). More advanced lymphomas reveal expansile, often destructive proliferations of neoplastic MZ cells "cavitating" preexisting benign lymphoepithelial lesions.

Immunohistochemistry shows that neoplastic cells bear the following profile: CD20+, IgM (>IgA > IgG) +, W>IgD-, CD5-, CD10-, BCL6-, and cyclin D1 (1, 7). Such phenotype allows to exclude mantle cell lymphoma and follicular lymphoma but is not per se pathognomonic. The IRTA1 monoclonal antibody is the only currently existing specific marker that reacts with more than 90 % EMZLs [60]. In particular, the "balls" of neoplastic cells growing within the lymphoepithelial lesions display very strong staining. Unfortunately, although extensively applied in some centers, the IRTA1 monoclonal antibody is not yet commercially available. Aberrant CD43 expression occurs in about half of the cases. In properly fixed material, monotypic restriction of Ig light chains is easily detected in both the perinuclear spaces of neoplastic cells and the associated plasma cell component, which also expresses IRF4/MUM1. The stains for CD21 and CD23 highlight remnants of follicular dendritic cells. Lastly, in case of follicular colonization, lymphomatous elements progressively lose IRTA1 and acquire BCL6 in the absence of CD10 staining [60]. The latter finding is indeed useful for distinguishing colonized follicles from residual follicles (CD10+ BCL6+).

PCR studies based on the BIOMED-2 approach detect a monoclonal Ig rearrangement in most, if not all, cases [58]. Ig sequencing shows a high load of somatic mutations, which can become ongoing in case of follicular colonization. Conversely to what is seen in lymphoplasmacytic lymphoma, MYD88 mutations rarely occur [61].

Three chromosomal translocations [t(11;18)(q21;q21)/API2-MALT1, t(14;18)(q32;q21)/IgH-MALT1, t(1;14)(p22;q32)/(IgH-BCL10)] can be detected in the ENMZLs of the salivary glands, while to the best of the authors' knowledge, the t(3;14)(p14;q32)/IgH-FOXP1 has not never been detected [58]. The three translocations seem to promote lymphoma development by a shared mechanism. In particular, they trigger NF-kB activation, a transcription factor that controls lymphocyte proliferation and apoptosis via the deregulation of BCL10 or MALT1 expression. The t(14;18)(q32;q21)/IgH-MALT1 represents the most commonly reported translocation in the setting of salivary gland MALT lymphoma, the remaining two being much rarer or even exceptional [58].

26.7 The Outcome of Patients with Sjögren Syndrome-Associated Lymphomas

The prognosis of lymphoma is widely variable depending on the histological subtype and grade as well as other factors such as disease stage. In general, low-grade lymphomas such as MALT lymphomas have a very good prognosis, and 5-year survival is approximately 90 %. On the other hand, aggressive forms like diffuse large B-cell lymphoma have a 5-year survival of 60 %.

Three relatively large studies examined the outcome of patients with SS-associated lymphomas [39, 40, 62].

In 1999, Voulgarelis et al. investigated the survival of 33 SS-related lymphoma patients categorized by histological subtype and showed that the median survival of patients with the high/intermediate histological grades was 1.83 years, while of low grades it was 6.33 years. The presence of B symptoms and largest tumor diameter >7 cm, along with histological classification, were associated with worse survival [40].

Pollard et al. explored the clinical course of patients with localized MALT lymphoma of the parotid gland that is linked to Sjögren syndrome. Lymphoma occurred in 35 cases out of 329 SS patients at a median follow-up of 76 months (range 16–153 months). Treatment was "watchful waiting" ($n=10$), surgery ($n=3$), radiotherapy ($n=1$), surgery combined with radiotherapy ($n=2$), rituximab alone ($n=13$), or rituximab combined with chemotherapy ($n=6$). Fourteen patients achieved complete CR, while stable disease was achieved by 20 patients and partial response by 1 patient. High SS disease activity was a poor prognostic factor for the progression of lymphoma and/or SS. The authors suggested that such patients should receive treatment despite having localized indolent lymphoma [62].

Papageorgiou and colleagues analyzed overall and event-free survival (OS and EFS) in the largest and most recent cohort of 77 SS-associated NHL patients. Events were lymphoma relapse, treatment failure, disease progression, histological transformation, or death. Ten patients died, five suffered a relapse, two experienced progression/transformation, and five patients developed other hematological malignancies that included T-cell NHL (two cases) and multiple myeloma, Hodgkin

disease, and thymoma (one case each). Seven of the deaths were due to neutropenic sepsis, two were due to relapse, and one death was attributed to reasons other than lymphoma or treatment-related causes. The 5-year OS and EFS for the entire NHL cohort was 90.91 % and 77.92 %, respectively. Depending on NHL subtypes, the 5-year OS was 94.12 % for MALT versus 87.5 % for NMZ, 75.0 % for DLBC, and 100 % for other lymphoma subtypes. The 5-year EFS was 86.27 % for patients with MALT, 62.5 % for patients with NMZ lymphoma, 50.0 % in DLBC lymphoma patients, and 83.3 % for other lymphoma subtypes. Survival differences between MALT and DLBC lymphomas were statistically significant [50]. The studies also revealed that the severity of SS disease (using the disease activity score) negatively impacts on the prognosis of NHL patients. Compared to patients with low SS disease activity, those with high disease activity had a greater risk of death (OR = 5.241) or of an event (OR = 4.317). Consequently, they had significantly worse EFS and OS. The authors also recognized additional predictors of lymphoma prognosis, such as an elevated the lymphoma international prognostic index (IPI) score and bone marrow involvement. After adjustment for identified risk factors, IPI score retained a significant effect on survival outcomes followed by a strong trend for SS disease activity score [50].

A diagnosis of lymphoma worsens expected survival in SS patients [32, 38, 51, 63]. Horvath and colleagues showed that having a lymphoproliferative disease during the course of SS disease increased the risk of mortality. Likewise, Voulgarelis and coworkers found that lymphoma was the main cause of death in patients with SS with a standardized mortality ratio of 3.25 in patients with lymphoma and 1.08 in patients without lymphoma [51].

A number of studies examined the outcome of SS-related lymphomas with specific types of therapy [39, 40, 64]. Ambrosetti and colleagues observed no significant differences in outcomes between SS patients with salivary MALT lymphomas who had undergone a variety of treatment modalities and those who were only observed [39]. This is consistent with a previous study which demonstrated that both SS and SS-associated salivary MALT lymphoma patients have a similar clinical course with a median overall survival of 6.4 years [40].

Voulgarelis and coauthors reported a 75 % CR rate with the purine analog 2-chloro-2-deoxyadenosine (2-CdA) in four SS-associated B-cell lymphoma patients during a 4-year follow-up. Interestingly, SS manifestations improved as well. Authors suggested that pronounced 2-CdA-induced T-cell depletion exerts an additional therapeutic effect in SS patients. Due to the small cohort and short follow-up, investigators could not come to any definitive conclusions on the therapeutic role of 2-CdA in SS-associated lymphoma [65].

Rituximab is a therapeutic agent used in the treatment of SS, with or without associated MALT lymphoma. Fifteen patients with primary SS were included in a phase II trial exploring the safety and efficacy of rituximab in SS patients ($n = 8$) and SS-related MALT lymphomas ($n = 7$). Of the seven patients with MALT lymphomas, CR was achieved in three, stable disease in three, while one patient progressed [64].

On the other hand, R-CHOP is the treatment of choice in SS-related aggressive NHL [66, 67]. Six SS patients with DLBC lymphoma were assigned to receive eight cycles of R-CHOP in a phase II trial. Patients were compared to a historic control of nine DLBC lymphoma patients treated with CHOP alone. A significant difference was observed in OS between the two groups, with a 2-year OS of 100 % in the R-CHOP-treated group versus 37 % in the control group. SS-related symptoms were also better in the study group, thus reflecting the immunogenic effect of rituximab on SS [67].

Conclusions

In summary, the risk of developing lymphoma in SS patients is considerably higher than in the general population. The majority of SS patients develop low-grade, usually ENMZ/MALT lymphoma subtype. High-grade DLBC lymphoma is seen in 10–15 % of SS-related lymphoma patients. The incidence of DLBC lymphoma seems to be underestimated in SS patients, and some studies showed that DLBC subtypes occur at rates similar to or even higher than that of low-grade lymphomas. Several clinical features and laboratory biomarkers are correlated to the risk of lymphoma in SS patients. However, there is currently not enough evidence to support their use in routine clinical practice. SS patients who are diagnosed with lymphoma have worse survival compared to SS patients who have no lymphoma. Studies on the mechanisms underlying lymphomagenesis in SS patients are ongoing.

References

1. Kassan SS, Moutsopoulos HM (2004) Clinical manifestations and early diagnosis of Sjogren syndrome. Arch Intern Med 164:1275–1284
2. Goules AV, Tzioufas AG, Moutsopoulos HM (2014) Classification criteria of Sjogren's syndrome. J Autoimmun 48–49:42–45
3. Weng MY, Huang YT, Liu MF, Lu TH (2011) Incidence and mortality of treated primary Sjogren's syndrome in Taiwan: a population-based study. J Rheumatol 38:706–708
4. Qin B, Wang J, Yang Z et al (2015) Epidemiology of primary Sjogren's syndrome: a systematic review and meta-analysis. Ann Rheum Dis 74:1983–1989
5. Reksten TR, Jonsson MV (2014) Sjogren's syndrome: an update on epidemiology and current insights on pathophysiology. Oral Maxillofac Surg Clin N Am 26:1–12
6. Nocturne G, Mariette X (2015) Sjogren syndrome-associated lymphomas: an update on pathogenesis and management. Br J Haematol 168:317–327
7. Quartuccio L, Isola M, Baldini C et al (2014) Biomarkers of lymphoma in Sjogren's syndrome and evaluation of the lymphoma risk in prelymphomatous conditions: results of a multicenter study. J Autoimmun 51:75–80
8. Valesini G, Priori R, Bavoillot D et al (1997) Differential risk of non-Hodgkin's lymphoma in Italian patients with primary Sjogren's syndrome. J Rheumatol 24:2376–2380
9. Youinou P, Mackenzie L, le Masson G et al (1988) CD5-expressing B lymphocytes in the blood and salivary glands of patients with primary Sjogren's syndrome. J Autoimmun 1:185–194
10. Hansen A, Daridon C, Dorner T (2010) What do we know about memory B cells in primary Sjogren's syndrome? Autoimmun Rev 9:600–603
11. Jonsson R, Nginamau E, Szyszko E, Brokstad KA (2007) Role of B cells in Sjogren's syndrome–from benign lymphoproliferation to overt malignancy. Front Biosci 12:2159–2170

12. Skarstein K, Nerland AH, Eidsheim M et al (1997) Lymphoid cell accumulation in salivary glands of autoimmune MRL mice can be due to impaired apoptosis. Scand J Immunol 46:373–378
13. Talal N, Sokoloff L, Barth WF (1967) Extrasalivary lymphoid abnormalities in Sjogren's syndrome (reticulum cell sarcoma, "pseudolymphoma," macroglobulinemia). Am J Med 43:50–65
14. Yamasaki S, Matsushita H, Tanimura S et al (1998) B-cell lymphoma of mucosa-associated lymphoid tissue of the thymus: a report of two cases with a background of Sjogren's syndrome and monoclonal gammopathy. Hum Pathol 29:1021–1024
15. Talal N, Bunim JJ (1964) The development of malignant lymphoma in the course of Sjoegren's syndrome. Am J Med 36:529–540
16. Talal N, Aufdemorte TB, Kincaid WL et al (1988) Two patients illustrating lymphoma transition and response to therapy in Sjogren's syndrome. J Autoimmun 1:171–184
17. Voulgarelis M, Skopouli FN (2007) Clinical, immunologic, and molecular factors predicting lymphoma development in Sjogren's syndrome patients. Clin Rev Allergy Immunol 32:265–274
18. Routsias JG, Goules JD, Charalampakis G et al (2013) Malignant lymphoma in primary Sjogren's syndrome: an update on the pathogenesis and treatment. Semin Arthritis Rheum 43:178–186
19. Smedby KE, Askling J, Mariette X, Baecklund E (2008) Autoimmune and inflammatory disorders and risk of malignant lymphomas – an update. J Intern Med 264:514–527
20. Zintzaras E, Voulgarelis M, Moutsopoulos HM (2005) The risk of lymphoma development in autoimmune diseases: a meta-analysis. Arch Intern Med 165:2337–2344
21. Tarella C, Gueli A, Ruella M, Cignetti A (2013) Lymphocyte transformation and autoimmune disorders. Autoimmun Rev 12:802–813
22. Martin DN, Mikhail IS, Landgren O (2009) Autoimmunity and hematologic malignancies: associations and mechanisms. Leuk Lymphoma 50:541–550
23. Smedby KE, Baecklund E, Askling J (2006) Malignant lymphomas in autoimmunity and inflammation: a review of risks, risk factors, and lymphoma characteristics. Cancer Epidemiol Biomarkers Prev 15:2069–2077
24. Kassan SS, Thomas TL, Moutsopoulos HM et al (1978) Increased risk of lymphoma in sicca syndrome. Ann Intern Med 89:888–892
25. Davidson BK, Kelly CA, Griffiths ID (1999) Primary Sjogren's syndrome in the North East of England: a long-term follow-up study. Rheumatology (Oxford) 38:245–253
26. Lazarus MN, Robinson D, Mak V et al (2006) Incidence of cancer in a cohort of patients with primary Sjogren's syndrome. Rheumatology (Oxford) 45:1012–1015
27. Zhang W, Feng S, Yan S et al (2010) Incidence of malignancy in primary Sjogren's syndrome in a Chinese cohort. Rheumatology (Oxford) 49:571–577
28. Pertovaara M, Pukkala E, Laippala P et al (2001) A longitudinal cohort study of Finnish patients with primary Sjogren's syndrome: clinical, immunological, and epidemiological aspects. Ann Rheum Dis 60:467–472
29. Theander E, Henriksson G, Ljungberg O et al (2006) Lymphoma and other malignancies in primary Sjogren's syndrome: a cohort study on cancer incidence and lymphoma predictors. Ann Rheum Dis 65:796–803
30. Kauppi M, Pukkala E, Isomaki H (1997) Elevated incidence of hematologic malignancies in patients with Sjogren's syndrome compared with patients with rheumatoid arthritis (Finland). Cancer Causes Control 8:201–204
31. Johnsen SJ, Brun JG, Goransson LG et al (2013) Risk of non-Hodgkin's lymphoma in primary Sjogren's syndrome: a population-based study. Arthritis Care Res (Hoboken) 65:816–821
32. Fallah M, Liu X, Ji J et al (2014) Autoimmune diseases associated with non-Hodgkin lymphoma: a nationwide cohort study. Ann Oncol 25:2025–2030
33. Anaya JM, McGuff HS, Banks PM, Talal N (1996) Clinicopathological factors relating malignant lymphoma with Sjogren's syndrome. Semin Arthritis Rheum 25:337–346
34. Nishishinya MB, Pereda CA, Munoz-Fernandez S et al (2015) Identification of lymphoma predictors in patients with primary Sjogren's syndrome: a systematic literature review and meta-analysis. Rheumatol Int 35:17–26

35. Ramos-Casals M, Solans R, Rosas J et al (2008) Primary Sjogren syndrome in Spain: clinical and immunologic expression in 1010 patients. Medicine (Baltimore) 87:210–219
36. Ramos-Casals M, Brito-Zeron P, Siso-Almirall A, Bosch X (2012) Primary Sjogren syndrome. BMJ 344:e3821
37. Baldini C, Pepe P, Quartuccio L et al (2014) Primary Sjogren's syndrome as a multi-organ disease: impact of the serological profile on the clinical presentation of the disease in a large cohort of Italian patients. Rheumatology (Oxford) 53:839–844
38. Solans-Laque R, Lopez-Hernandez A, Bosch-Gil JA et al (2011) Risk, predictors, and clinical characteristics of lymphoma development in primary Sjogren's syndrome. Semin Arthritis Rheum 41:415–423
39. Ambrosetti A, Zanotti R, Pattaro C et al (2004) Most cases of primary salivary mucosa-associated lymphoid tissue lymphoma are associated either with Sjoegren syndrome or hepatitis C virus infection. Br J Haematol 126:43–49
40. Voulgarelis M, Dafni UG, Isenberg DA, Moutsopoulos HM (1999) Malignant lymphoma in primary Sjogren's syndrome: a multicenter, retrospective, clinical study by the European concerted action on Sjogren's syndrome. Arthritis Rheum 42:1765–1772
41. Muller K, Oxholm P, Mier-Madsen M, Wiik A (1989) Circulating IgA- and IgM-rheumatoid factors in patients with primary Sjogren syndrome. Correlation to extraglandular manifestations. Scand J Rheumatol 18:29–31
42. Brito-Zeron P, Ramos-Casals M, Nardi N et al (2005) Circulating monoclonal immunoglobulins in Sjogren syndrome: prevalence and clinical significance in 237 patients. Medicine (Baltimore) 84:90–97
43. Brito-Zeron P, Kostov B, Solans R et al (2014) On behalf of the SS Study Group, Autoimmune Diseases Study Group (GEAS), Spanish Society of Internal Medicine (SEMI). Systemic activity and mortality in primary Sjogren syndrome: predicting survival using the EULAR-SS Disease Activity Index (ESSDAI) in 1045 patients. Ann Rheum Dis doi:10.1136/annrheumdis-2014-206418
44. Theander E, Vasaitis L, Baecklund E et al (2011) Lymphoid organisation in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjogren's syndrome. Ann Rheum Dis 70:1363–1368
45. Risselada AP, Kruize AA, Goldschmeding R et al (2014) The prognostic value of routinely performed minor salivary gland assessments in primary Sjogren's syndrome. Ann Rheum Dis 73:1537–1540
46. Baimpa E, Dahabreh IJ, Voulgarelis M, Moutsopoulos HM (2009) Hematologic manifestations and predictors of lymphoma development in primary Sjogren syndrome: clinical and pathophysiologic aspects. Medicine (Baltimore) 88:284–293
47. Smedby KE, Hjalgrim H, Askling J et al (2006) Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. J Natl Cancer Inst 98:51–60
48. Vasaitis L Nordmark G, Askling J, Ekström-Smedby K, Backlin C, Rönnblom L (2012) Diffuse large B-cell lymphoma. An underestimated subtype and cause of death in primary Sjögren's syndrome. Abstract EULAR
49. Tonami H, Matoba M, Kuginuki Y et al (2003) Clinical and imaging findings of lymphoma in patients with Sjogren syndrome. J Comput Assist Tomogr 27:517–524
50. Papageorgiou A, Ziogas DC, Mavragani CP et al (2015) Predicting the outcome of Sjogren's syndrome-associated non-hodgkin's lymphoma patients. PLoS ONE 10:e0116189
51. Voulgarelis M, Ziakas PD, Papageorgiou A et al (2012) Prognosis and outcome of non-Hodgkin lymphoma in primary Sjogren syndrome. Medicine (Baltimore) 91:1–9
52. Jaffe ES (2009) The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. Hematol Am Soc Hematol Educ Prog 2009:523–531
53. Revanappa MM, Sattur AP, Naikmasur VG, Thakur AR (2013) Disseminated non-Hodgkin's lymphoma presenting as bilateral salivary gland enlargement: a case report. Imaging Sci Dent 43:59–62

54. Mian M, Capello D, Ventre MB et al (2014) Early-stage diffuse large B cell lymphoma of the head and neck: clinico-biological characterization and 18 year follow-up of 488 patients (IELSG 23 study). Ann Hematol 93:221–231
55. Anacak Y, Miller RC, Constantinou N et al (2012) Primary mucosa-associated lymphoid tissue lymphoma of the salivary glands: a multicenter rare cancer network study. Int J Radiat Oncol Biol Phys 82:315–320
56. Shashidara R, Prasad PR, Jaishankar JT (2014) Follicular lymphoma of the submandibular salivary gland. J Oral Maxillofac Pathol 18:S163–S166
57. Agaimy A, Wild V, Markl B et al (2015) Intraparotid classical and nodular lymphocyte-predominant hodgkin lymphoma: pattern analysis with emphasis on associated lymphadenoma-like proliferations. Am J Surg Pathol 39:1206–1212
58. Bacon CM, Du MQ, Dogan A (2007) Mucosa-associated lymphoid tissue (MALT) lymphoma: a practical guide for pathologists. J Clin Pathol 60:361–372
59. Zinzani PL (2012) The many faces of marginal zone lymphoma. Hematol Am Soc Hematol Educ Prog 2012:426–432
60. Falini B, Agostinelli C, Bigerna B et al (2012) IRTA1 is selectively expressed in nodal and extranodal marginal zone lymphomas. Histopathology 61:930–941
61. Voulgarelis M, Mavragani CP, Xu L et al (2014) Absence of somatic MYD88 L265P mutations in patients with primary Sjogren's syndrome. Genes Immun 15:54–56
62. Pollard RP, Pijpe J, Bootsma H et al (2011) Treatment of mucosa-associated lymphoid tissue lymphoma in Sjogren's syndrome: a retrospective clinical study. J Rheumatol 38:2198–2208
63. Horvath IF, Szanto A, Papp G, Zeher M (2014) Clinical course, prognosis, and cause of death in primary Sjogren's syndrome. J Immunol Res 2014:647507
64. Pijpe J, van Imhoff GW, Spijkervet FK et al (2005) Rituximab treatment in patients with primary Sjogren's syndrome: an open-label phase II study. Arthritis Rheum 52:2740–2750
65. Voulgarelis M, Petroutsos G, Moutsopoulos HM, Skopouli FN (2002) 2-chloro-2′-deoxyadenosine in the treatment of Sjogren's syndrome-associated B cell lymphoproliferation. Arthritis Rheum 46:2248–2249
66. Voulgarelis M, Giannouli S, Tzioufas AG, Moutsopoulos HM (2006) Long term remission of Sjogren's syndrome associated aggressive B cell non-Hodgkin's lymphomas following combined B cell depletion therapy and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). Ann Rheum Dis 65:1033–1037
67. Voulgarelis M, Giannouli S, Anagnostou D, Tzioufas AG (2004) Combined therapy with rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) for Sjogren's syndrome-associated B-cell aggressive non-Hodgkin's lymphomas. Rheumatology (Oxford) 43:1050–1053