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Presentation, Characteristics and Features of Lymphoma in a Retrospective Case Series of Patients with Sjogren's Disease

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Abstract: Sjogren's Disease (SjD) is associated with an increased risk of lymphoma. We investigated the prevalence of lymphoma in a retrospective case series of patients with SjD and reported on the clinical presentation, treatment, response, and outcome. A retrospective review of 132 patients diagnosed with Sjogren's Disease was conducted at our institution from June 2000 to November 2023, and 10 cases of malignant lymphoma were identified. Clinical and biological markers known to be predictors of lymphoma, as well as lymphoma characteristics, were examined. The most common predictive lab findings were hypergammaglobulinemia, the rheumatoid factor, and lymphopenia. Persistent parotid gland enlargement was also found in greater than 50% of patients. The majority of patients were Caucasian females, and the average time between the diagnosis of SjD and lymphoma was 14.3 years. The median age at lymphoma diagnosis was 59.5 years, with 9 out of 10 lymphomas identified as non-Hodgkin lymphoma, the majority of cases being mucosa-associated lymphoid tissue (MALT) lymphoma. We identified similarities in our series, such as laboratory markers and clinical symptoms, to those previously identified as possible predictors of lymphoma development. These factors may be useful in determining the risk of malignancy development and justify the need for long-term monitoring, as well as provider education and awareness.

Keywords: Sjogren's disease (SjD); lymphoma; parotid gland

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1. Introduction

Sjogren's Disease (SjD) is a chronic autoimmune disease defined by the lymphocytic infiltration of the exocrine glands, leading to their destruction and ultimately presenting predominantly with dry eyes and dry mouth [1]. SjD may develop independently or in conjunction with another autoimmune condition, such as systemic lupus erythematosus, rheumatoid arthritis, or scleroderma. There is a well-known relationship between SjD and an increased risk of lymphoma, with previous reports finding the incidence of non-Hodgkin lymphoma (NHL) highest in SjD than all other autoimmune diseases [2,3]. The risk of lymphoma has been thought to be 4–16-fold higher in these patients than in the general population [3–6]. It has been hypothesized that the chronic inflammatory pathway seen in Sjogren's Disease triggers B cell activation, potentially leading to the increased production of B lymphocytes and the eventual development of malignancy [7].

Indolent marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type has been recognized by several studies as the most common lymphoma subtype in SjD [8]. The development of NHL may occur in 5–7% of SjD patients, usually within 10 years of diagnosis [9,10]. However, there is variability from the diagnosis of SjD to the diagnosis of lymphoma, with some lymphomas diagnosed at the onset of SjD symptoms, while others have been reported as late as 36 years after disease onset [9]. Some studies have shown that lymphoma may be one of the main causes of death in SjD [11]. Reported mortality rates from lymphomas vary among different SjD patient groups, with the highest

being in the 23–33% range [9,12]. Since malignant lymphoma is the main complication with a considerable impact on survival, it is important to identify the characteristics of SjD patients with lymphoma to help aid in early diagnosis and intervention. In this study, we investigate the prevalence of lymphoma in a series of patients with SjD and report on the clinical and laboratory presentation, response to treatment, and outcomes.

2. Materials and Methods

A medical records review of 132 patients diagnosed with primary Sjogren's Disease was performed at our institution from the time period of June 2000 to November 2023, with 10 cases of malignant lymphoma identified. Data recorded on each patient includes sex, ethnicity, age at SjD diagnosis, the presence of anti-Ro (Sjogren's Syndrome A, SSA) and anti-La (Sjogren's Syndrome B, SSB), extraglandular manifestations, age at lymphoma diagnosis, the interval between the diagnosis of SjD and lymphoma, site of presentation, clinical staging, the lymphoma subtype, and final outcome (remission, relapse, progression of disease, and death). The lymphoma subtype was classified according to the 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms [13].

We also recorded the clinical and serological features associated with lymphoma risk. The clinical predictors included persistent swelling of the parotid glands, peripheral neuropathy, splenomegaly, and palpable purpura. Lab abnormalities thought to be predictors of lymphoma include the presence of lymphopenia, defined as an absolute lymphocyte count $< 1000/mm^3$, hypergammaglobulinemia, circulating monoclonal proteins in serum or urine, cryoglobulinemia, hypocomplementemia (C4) and the presence of a rheumatoid factor (RF), anti-nuclear antibody (ANA), SSA, or SSB.

3. Results

In our series, 10 out of 132 patients (7.6%) developed lymphoma. The clinical and epidemiological features are displayed in Table 1. The demographics of the lymphoma patients included 9 females and 1 male. The ethnicity breakdown is as follows: 6 Caucasians, 2 African Americans, 1 Asian/Indian, and 1 Hispanic patient. The mean age at diagnosis of Sjogren's Disease was 44.9 years $\pm$ 10.2 with a range of 32–67. The mean age at lymphoma diagnosis was 58.5 years $\pm$ 12.6 with a range of 36–74, while the mean interval between SjD diagnosis and the development of lymphoma was 14.3 years $\pm$ 7.9 with a range of 1–25.

At the time of SjD diagnosis, 90% of our series had a positive SSA antibody, 50% had SSB, and one patient was seronegative. In total, 50% of our series was positive for both SSA and SSB antibodies. Prior to the development of lymphoma, 50% of our patients had parotid enlargement, 1 patient had parotitis, and 1 patient had parotid abscess. All of our patients demonstrated at least one extraglandular manifestation (EGM) of SjD ranging from 1 to 4 EGM with a mean of 2.1 EGM. In total, 4 patients had inflammatory polyarthritis, 4 had bronchiectasis, 3 had peripheral neuropathy, 2 had renal tubular acidosis (RTA) with nephrocalcinosis, and 1 had tubulointerstitial nephritis.

Based on the 2016 WHO classification, 9 out of the 10 lymphomas were of the non-Hodgkin subtype, all of which were of B-cell origin. A review of the pathology reports revealed 5 cases of the extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) types, 1 nodal marginal zone (MZL) type, 3 cases of diffuse large B cell lymphoma (DLBCL), and 1 patient with Hodgkin lymphoma at nodular sclerosis subtype stage IVB. Within our series, patients with MALT lymphoma were diagnosed at an earlier age as opposed to patients with non-MALT lymphoma. The average age of MALT lymphoma was 50.8 years $\pm$ 11.37, while the average age of non-MALT lymphoma diagnosis was 67.8 years $\pm$ 7.6 ($p = 0.03$).

Table 1. Clinical and epidemiological features of SjD patients with lymphoma.

Case/Sex/ Ethnicity	Age at SjD Diagnosis	Anti-Ro/SSA Anti-La/SSB	Time (Years) from SjD Diagnosis	Lymphoma Subtype	Presentation and Site of Lymphoma	Glandular SjD Manifestations	Extraglandular SjD Manifestations	Comorbidities
1/F/Hispanic	41	Positive/Positive	1	MALT	Asymmetrical enlargement of parotid gland	XF, XS, PGE	Polyarthritis	None
2/F/Caucasian	32	Positive/Positive	4	MALT	Bilateral cervical lymphadenopathy	XS, PGE, parotitis	Anemia, bronchiectasis, polyarthritis, RP	SLE, IBM, sarcoidosis, GERD
3/F/AA	67	Positive/Negative	7	NSHL stage IVB	B-symptoms, supraclavicular LN, para-aortic LN	XS, PGE	Neuropathy	Hypothyroidism
4/F/Caucasian	51	Negative/Negative	21	MZL	B-symptoms, monoclonal gammopathy, inguinal LN	XF, XS	Bronchiectasis, interstitial fibrosis, nephrocalcinosis	IBD
5/M/Caucasian	32	Positive/Negative	23	DLBCL, stage III	B-symptoms, parotid gland enlargement, cervical LN, mediastinal LN, axillary LN, inguinal LN, retroperitoneal LN	XF, XS, PGE	VL, RP	Hypothyroidism
6/F/AA	42	Positive/Positive	17	MALT	Conjunctival mass, ocular inflammation, weight loss/lacrimal gland	XF, XS	Bronchiectasis, pulmonary fibrosis, synovitis, neuropathy	SLE, cryoglobulinemia GN
7/F/Caucasian	40	Positive/Positive	14	MALT	Intraglandular palpable mass followed by diffuse lymphadenopathy/Axillary LN	XF, XS, sialadenitis	Neuropathy, VL	AH
8/F/Caucasian	56	Positive/Negative	11	DLBCL, stage IV	Upper abdominal pain, anorexia, weight loss, LUQ mass	XS, XF, PGE	Polyarthritis	HLD, HTN, breast cancer
9/F/Caucasian	46	Positive/Negative	25	DLBCL, stage 1AE, in CR	LUQ pain, gastric mass on EGD	XS, XF, Parotid abscess	Tubulointerstitial nephropathy/RTA, nephrocalcinosis	SCAD with vfib arrest, melanoma
10/F/Asian Indian	42	Positive/Positive	20	Pulmonary MALT lymphoma	Incidental finding on CT chest, RML mass and RLL nodule	XS, XF	Polyarthritis	HLD, GERD, vasovagal syncope

AA, African American; AH, autoimmune hepatitis; MALT, mucosa-associated lymphoid tissue lymphoma; NSHL, nodular sclerosing Hodgkin's lymphoma; DLBCL, diffuse large B cell lymphoma; GN, glomerulonephritis; IBD, inflammatory bowel disease; HLD, hyperlipidemia; GERD, gastroesophageal reflux disease; IBM, inclusion body myositis; PGE, parotid gland enlargement; SjD, Sjogren's Disease; SLE, systemic lupus erythematosus; RP, Raynaud's phenomenon; SCAD, sudden coronary artery dissection; vfib, ventricular fibrillation; VL, biopsy-proven cutaneous vasculitis; XS, xerostomia; XF, xerophthalmia; LN, lymph node; LUQ, left upper quadrant; RML, right middle lobe; RLL, right lower lobe; and EGD, esophagogastroduodenoscopy.

The clinical presentation of each lymphoma can be seen in Table 1. These include the asymmetrical enlargement of the parotid or lacrimal glands, an intraglandular palpable mass followed by diffuse lymphadenopathy, monoclonal gammopathy, peripheral lymph node enlargement, and B-symptoms (fever, night sweats, and weight loss). The primary site of malignancy varied amongst patients. Overall, 1 patient had an incidental lung mass/nodule on chest computed tomography (CT), 2 patients had a left upper quadrant mass, 4 had glandular manifestations, and 4 patients had lymphadenopathy. Of the patients with glandular manifestations, 1 had a conjunctival mass and ocular inflammation, while 3 patients had parotid enlargement and/or a palpable mass. The location of lymphadenopathy varied and included the following sites: cervical, supraclavicular, mediastinal, axillary and inguinal. In total, five patients had B-symptoms (fever, night sweats, and weight loss). Additionally, staging at the time of lymphoma diagnosis disclosed the fact that the disease was limited to the primary site in 8 cases, while in 2 cases, the disease had already spread (stages III and IV).

Previously identified clinical and lab factors associated with the risk of lymphoma are summarized in Table 2. The most prevalent clinical feature in our series was parotid enlargement (7 cases). Hypergammaglobulinemia and the presence of the rheumatoid factor were both found in 6 out of the 10 patients, while lymphopenia was found in 5 out of 10 patients.

Table 2. Clinical and laboratory risk factors associated with the development of lymphoma.

	Case 1/F	**Case 2/F**	**Case 3/F**	**Case 4/F**	**Case 5/M**	**Case 6/F**	**Case 7/F**	**Case 8/F**	**Case 9/F**	**Case 10/F**
Persistent enlargement of parotid glands	+	+	−	−	+	+	+	+	+	−
Peripheral neuropathy	−	−	+	−	−	+	+	−	−	−
Palpable purpura	−	−	−	−	+	−	−	−	−	−
Splenomegaly	−	−	−	−	+	−	−	−	−	−
ANA positivity	+	+	+	+	+	+	+	+	+	+
Rheumatoid factor positivity	+	NA	−	+	+	NA	+	+	−	+
Lymphopenia [1]	−	+	−	+	−	+	+	−	+	−
Monoclonal proteins in serum and/or urine	−	−	+	+	−	−	−	−	+	−
Low C4	−	+	NA	−	+	+	−	−	−	−
Elevated immunoglobulins	−	+	+	−	+	+	+	−	−	+
Cryoglobulinemia	−	−	−	−	NA	+	−	−	−	−

[1] Lymphopenia was defined as an absolute lymphocyte count < 1000/mm^3. + Risk factor present; − Risk factor absent; NA, data not available. ANA, anti-nuclear antibody.

Seven patients were treated with either rituximab, chemotherapy, or complementary radiotherapy, while the other three were monitored for the evolution of disease (MALT lymphoma and nodal marginal zone type). Complete remission was achieved in 3 MALT lymphoma cases and 1 DLBCL after initial treatment, as seen in Table 3. Partial response was seen in 1 MALT lymphoma after rituximab. In total, 4 out of the 10 patients had a relapse of their lymphoma. In total, 1 patient expired as a result of lymphoma, while 4 of 10 patients expired due to illnesses that were not directly related to their lymphoma diagnosis.

Table 3. Classification of lymphoma, its treatment, and disease progression.

Case/Sex	Age at Lymphoma Diagnosis	Lymphoma Subtype	Initial Induction Therapy	Duration	Response to Therapy	Age at Relapse (Years)	Number of Relapses/ Location	Treatment at Relapse	Response to Therapy	Follow-Up Period (mo)	Disease Evolution
1/F	42	MALT	Rituximab	4 weeks	PR	43	1/parotid gland and lip nodule	Rituximab	CR	202	Free of disease
2/F	36	MALT	3000 cGY to right neck over 15 fractions	2 weeks	CR	41, 58	1/parotid gland and 2/parotid gland	1/radiation and 2/resection of gland and rituximab	CR	312	Death unrelated to disease progression
3/F	74	NSHL stage IVB	R-CHOP	6 months	CR	88	1/intrathoracic lymph nodes	Prednisone	PR	264	On maintenance treatment
4/F	72	MZL	Surveillance	-	-	-	-	-	-	12	Death unrelated to disease progression
5/M	55	DLBCL, stage III	CHOP	1 month	NR	-	-	-	-	2	Death by disease progression
6/F	59	MALT	Rituximab	weeks	CR	59	1/lacrimal	Rituximab	CR	24	Death unrelated to disease progression
7/F	54	MALT	Surveillance	-	-	-	-	-	-	165	Free of disease
8/F	67	DLBCL stage IV	RCHOP	4 months	CR	-	-	-	CR	30	Free of disease
9/F	71	DLBCL, stage 1AE	RCHOP	6 months	CR	-	-	-	-	21	Death unrelated to disease progression
10/F	65	Pulmonary MALT lymphoma	Surveillance	-	-	-	-	-	-	22	Under surveillance

MALT, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; NSHL, nodular sclerosing Hodgkin's lymphoma; MZL, B cell marginal zone lymphoma; DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine, prednisolone; CR, complete remission, NR, no response; and PR, partial remission. Follow-up period (mo) since lymphoma diagnosis.

4. Discussion

The prevalence of lymphoma in our SjD patients was comparable to estimates of approximately 5–8% reported in other studies [10]. SjD, like many autoimmune disorders, exhibits a higher prevalence in females [14]. Within our series, there was only one male patient. Interestingly, this patient exhibited the highest number of suggested predictors associated with the development of lymphoma, as can be seen in Table 2. He was also the only patient to expire as a result of lymphoma progression. In addition to palpable purpura, this patient presented with parotid gland swelling and low complement four levels. This case not only underscores the role of these risk factors in lymphoma development but also suggests a potential association between disease activity, progression, and sex. A study completed in Korea investigating the extraglandular manifestations of SjD in men found a notably higher prevalence of lymphoma among males compared to females (9.1% vs. 0.3%, $p = 0.002$) [15]. Anaya et al. reported the prevalence of lymphoma in males with isolated SjD to be as high as 15.4% [16]. This further supports the idea that sex plays a role in disease manifestations, and males may have a higher than suspected risk of lymphoma development.

Age has also been thought to play a part in lymphoma development. A study by Ramos-Casals et al. showed that patients who developed SjD earlier in life had a greater risk of lymphoma development, though subsequent studies did not support this theory [17]. A more recent study involving 1997 patients by Goules et al. revealed that those with disease onset before the age of 35 or after age 65 had an increased incidence of lymphoma compared to those diagnosed with Sjogren's Disease between ages 36 and 64 [18]. Although Goules' study highlighted a bimodal age distribution, the majority of our patients were diagnosed between ages 35 and 64.

The clinical manifestations that have been associated with lymphoma risk include the persistent enlargement of the parotid or lacrimal glands, chronic lymphadenopathy, palpable purpura, splenomegaly, and peripheral neuropathy [19–21]. Early studies have indicated that persistent parotid gland swelling is associated with an increased risk of lymphoma. The relative risk (RR) of lymphoma development in these patients is 66.7, as opposed to 12.5 for SjD patients without parotid enlargement [22]. Moreover, findings from a large multicenter Italian study suggest that the significance of parotid swelling is dependent on the coexpression of laboratory markers, such as leukopenia, low C4 levels, positive SSA/SSB, or cryoglobulinemia. This study reported that the presence of 2 out of these 4 biomarkers in patients with parotid gland swelling correlated with a nine-fold increase in lymphoma risk, while the absence of any markers yielded a negative predictive value of approximately 90% [23]. Within our series, 7 out of 10 patients exhibited persistent parotid swelling, all of whom also presented with at least two additional predictive prognostic factors.

Laboratory findings that have been associated with lymphoma development include ANA positivity, the rheumatoid factor (RF), the presence of lymphopenia defined as an absolute lymphocyte count <1000/mm^3, hypergammaglobulinemia, circulating monoclonal proteins in serum or urine, cryoglobulinemia, and hypocomplementemia [19–21]. In the cellular pathway involved in the lymphomagenesis of Sjogren's Disease, abnormal B-cell maturation leads to the generation of self-reactive B-cells. This prolonged survival of autoreactive B-cells leads to the production of autoantibodies and the rheumatoid factor, which are thought to be associated with lymphoma development [24]. Prior to a study in 2015, an association between the presence of rheumatoid factors and the development of lymphoma had not been reported. In a study by Nocturne et al., the rheumatoid factor was detected in approximately two-thirds of lymphoma patients, suggesting its potential use as a predictive marker. Given that RF is easy to obtain and cost-effective compared to other assays, such as cryoglobulins, it holds promise for patient monitoring [21]. In our series, 60% of patients had a positive rheumatoid factor, further supporting its utility as a risk factor for lymphoma development in this patient population.

Because the prevalence of ANA in SjD is estimated to be as high as 80%, it is difficult to evaluate the sensitivity of ANA as a predictive marker [25,26]. Nevertheless, studies, including that by Wan et al., have indicated an increased prevalence of positive ANA in lymphoma patients independent of SjD, suggesting a potential relationship between ANA positivity and lymphomagenesis [27]. A recent study by Frost et al. observed that a positive ANA was associated with a higher risk of developing DLBCL. Stratified analyses suggest that this association may even be stronger in males compared to females. Although no association between ANA and other subtypes of lymphoma aside from DLBCL was found in their study, anti-SSA and anti-dsdna were found to be associated with DLBCL and MZL [28].

Lymphopenia has been observed more frequently in SjD patients who develop lymphoma [29]. In a study by Fragkioudaki, SjD NHL occurrence was associated with lymphopenia (28.3% in patients with NHL vs. 11.6% in SjD patients without a diagnosis of lymphoma, $p < 0.001$) [30]. Similarly, Baimpa et al. reported the presence of lymphopenia as a risk factor for the development of non-MZBCLs (marginal zone B-cell lymphomas), particularly DLBCL ($p = 0.044$) [10]. In our series, 50% of patients exhibited lymphopenia. However, among these patients, only one developed DLBCL, while three had MALT, and one developed MZL. Although our findings do not align with previous studies regarding the lymphoma subtype, lymphopenia remains a significant hematologic abnormality potentially indicative of disease development.

Malignancies, particularly lymphoma and lymphoproliferative disorders, are commonly associated with polyclonal hypergammaglobulinemia. This abnormality is also prevalent in autoimmune diseases and is one of the most common hematologic manifestations found in SjD, thought to be a direct result of continuous IL-6 stimulation and B cell activation [10,31,32]. Hypergammaglobulinemia also correlates with extraglandular manifestations, such as splenomegaly [10]. Moreover, there is a perceived association between hypergammaglobulinemia, RF positivity, and the presence of both SSA and SSB [33,34]. This suggests that these markers may collectively hold predictive value for malignancy development. In our study, 6 out of 10 patients exhibited elevated immunoglobulin levels. However, all of these patients also presented with at least two additional potential predictive markers alongside hypergammaglobulinemia.

There is notable diversity in the progression of lymphoproliferative disorders in SjD, which encompasses several lymphoma subtypes observed in prior studies and in our data. The predominant subtypes, accounting for more than 90% of reported cases in primary Sjogren's Disease, include MALT lymphoma, DLBCL, and MZL [10]. Most studies indicate that the most common type of lymphoma seen in SjD is MALT lymphoma [3,35,36], as was seen in our patients. In total, 50% had MALT, while 30% were diagnosed with DLBCL, 10% had NSHL, and 10% had MZL. MALT lymphoma generally carries a more favorable prognosis compared to DLBCL in isolated Sjogren's Disease [37]. The relative risk of developing lymphoma for SjD is estimated to be up to 16 times higher than the general population [31]. The risk of lymphoma development is maintained at high levels even 10–15 years after SjD diagnosis [38]. And it appears to increase with disease duration, with the cumulative risk of developing lymphoma at around 3.4% in the first 5 years and approximately 9.8% within 15 years after initial SjD diagnosis [31]. Our data show that out of the 10 patients who were diagnosed with lymphoma, 2 were diagnosed within 5 years of their initial SjD diagnosis, 3 were diagnosed within 5–15 years after their SjD diagnosis, and 5 were diagnosed more than 15 years after their SjD diagnosis. Furthermore, while the mean time between SjD diagnosis and the development of lymphoma in our series was 14.3 years $\pm$ 7.9, the duration of time ranged from 1 year to 25 years, further supporting the need for long-term monitoring. Additionally, within our series, patients with MALT lymphoma were diagnosed at an earlier age, as opposed to patients with non-MALT lymphoma.

This high-risk population should undergo regular screening for lymphoma risk features. Some have suggested biannual monitoring with clinic visits and comprehensive

laboratory assessments, which may include a complete blood count, ANA, RF, quantitative immunoglobulins, C4, assessment for monoclonal gammopathy, and cryoglobulins. On average, our patients who developed lymphoma had 3.3 of these laboratory findings. A physical exam should also focus on parotid gland swelling, peripheral neuropathy, palpable purpura, and splenomegaly. Since lymphoma presentation was variable, with patients demonstrating persistent swelling of the parotid gland, conjunctival mass, lymphadenopathy, and abdominal pain, additional concern should be paid to these regions.

The limitations of our study included a small sample size of 10 patients with lymphoma. This study was also retrospective, and some laboratory assays were not collected for all patients.

5. Conclusions

Approximately 1 out of every 5 deaths in patients with SjD is caused by lymphoma [9,39]. Our series appears to be representative of the prevalence, associated risk factors, and clinical presentation of the development of lymphoma in Sjogren's Disease. This includes less-appreciated presentations involving the ocular conjunctiva, abdomen, and lung. The sustained risk justifies the need for long-term monitoring of features of lymphoma, as well as providing education and awareness in order to achieve the early diagnosis of a potentially lethal malignancy.

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