

PRIMARY SJÖGREN'S SYNDROME AND THE RISK FOR DEVELOPING LYMPHOMAS

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Abstract. *In its course, primary Sjögren's syndrome marks an increased risk for developing lymphomas. Compared to healthy population, this risk can reach a 44-fold higher frequency. In the case of a relatively calm course of the disease, a „break“ in the clinical picture may occur and the manifestations of malignant lymphoma may develop. However, there are clinical and laboratory abnormalities of varying duration, which, with their summation over time, shorten the path to malignant lymphoproliferation. The identification of groups of patients at an increased risk for developing lymphomas and their follow-up is the basis of the personalized approach in patients with Sjögren's syndrome.*

Key words: *primary Sjögren's syndrome, risk of lymphomas*

Primary Sjögren's syndrome is a systemic autoimmune disease with diverse clinical manifestations – from sicca syndrome (xerostomia and xerophthalmia) to severe systemic disorders. In its course, the disease marks the following features:

1. Deterioration of quality of life
2. Shortened survival
3. Increased risk for developing oncological diseases – solid tumors and hemoblastoses
4. Increased risk for developing non-Hodgkin's lymphomas (NHLs) – 7 times higher compared to patients with secondary Sjögren's syndrome in systemic lupus erythematosus, 4 times higher in concomitant rheumatoid arthritis and 10 times higher compared to healthy individuals.

A key role in the development of lymphomas plays the constant B-cell stimulation by autoantibodies and various exogenous infectious factors. The state of B-cell hyperstimulation is the leading cause for the emergence of a pathological cell line and the development of malignant lymphoproliferation [1].

The degree of the risk for developing lymphomas is calculated by using a standardized morbidity ratio (SMR), which is the ratio of lymphomas in patients with primary Sjögren's syndrome to the estimated number of lymphomas in the general population.

For the first time in 1978, S. S. Kassan et al. considered the existence of a relationship between the primary forms of the disease and the development of lymphomas [2]. The development of NHL in primary Sjögren's syndrome was later shown to be 44.4 times more frequent in the US, and the development of NHL in SSj and rheumatoid arthritis showed a 42.9 times higher incidence rate according to the US data.

A significant number of studies were conducted to analyze the degree of the risk for developing lymphomas in primary Sjögren's syndrome. Due to the different designs of the clinical studies, divergent results were obtained [3].

However, the standardized morbidity ratio in recent years has fluctuated from 10.5 to 48.1, due to a certain extent to a change in the ICD codes of diseases, as well.

Lymphomas are the main type of neoplasms in patients with primary Sjögren's syndrome, and are presented in different classifications, with revisions and updates over the years.

According to the WHO, the main types of lymphomas are the B-cell and T/NK-cell types.

Clinical manifestations vary according to the histological variant and organ involvement. According to their progression, lymphomas are defined as:

1. Indolent lymphomas (MALT lymphoma, follicular type lymphomas, chronic lympholeukosis, lymphomas of the marginal zone of the spleen).
2. Aggressive lymphomas (diffuse B-cell type, Burkitt's lymphoma, acute lymphoblastic leukemia and most of the T-cell lymphomas with characteristic systemic symptoms).

In primary Sjögren's syndrome, B-cell type lymphomas predominate. A meta-analysis of 22 clinical studies found that only 2% of 598 patients, diagnosed with lymphoma, developed T-cell lymphomas.

In 90% of the cases, one of the following three types of lymphomas is diagnosed:

1. MALT lymphoma
2. Diffuse large B-cell lymphoma
3. Lymphoma of the marginal zone of the spleen
4. Myeloma in monoclonal gammopathy

5. Non-B-cell hemopathies – Hodgkin's disease, T-cell lymphomas.

MALT lymphomas predominate and account for up to 63% of hemopathies in primary Sjögren's syndrome (with the most common localization in parotid glands) [4].

MALT lymphomas usually have a single localization, but there are multifocal forms with simultaneous involvement of the stomach, skin and other organs.

Due to the fact that in 20% of the cases MALT lymphomas may have more than a single extranodal localization, it is always necessary to carry out a complex examination with several imaging methods (CAT, MRI).

In 10% of the patients with diagnosed lymphoma, the prognosis is serious, due to the involvement of lymph nodes in many areas, as well as the presence of lymphoma cells in the bone marrow (leukemization of the lymphoma).

MALT lymphomas may transform into diffuse large B-cell lymphomas [5].

MALT lymphomas represent the most common type of lymphomas in primary Sjögren's syndrome. They can arise from various extranodal areas. Usually, there is chronic antigenic stimulation (auto-antigens, H. pylori, HCV) during the course of the disease. The different types of MALT lymphoma show definite cytological expression (localization in the lungs, salivary glands, thyroid gland, skin). In general, MALT lymphomas have a small number of clinical manifestations, a slow course, and a good survival rate [6].

V. Voulgarelis et al. provided the first comprehensive characterization of lymphomas associated with primary Sjögren's syndrome, with an included database from 9 European centers [7]. It was found that 36% of the patients had extranodal lymphomas,

45% – nodal and extranodal lymphomas, and 18% – nodal localization.

According to the degree of differentiation, it was found that 70% of the cases were low-differentiated forms. In 69% of the patients, the localization of lymphomas with extranodal involvement was in the salivary glands. Salivary gland lymphoma accounts for less than 5% of all types of lymphomas and is between 5-10% of all salivary gland neoplasms.

MALT lymphomas with predominant localization are of the salivary glands, of the stomach.

In the course of observation, it is important to determine which of the patients with primary Sjögren's syndrome have an increased risk for developing lymphomas. Screening of the monitored cohort is needed.

Due to the chronic antigenic irritation and the increased risk for developing lymphomas, the place of personalized medicine is emphasized, with the earliest diagnostic and best therapeutic solutions for each patient with primary Sjögren's syndrome, and an individual approach [8].

PROGNOSTIC FACTORS OF THE RISK FOR DEVELOPING LYMPHOMAS IN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME

G. Clark et al. evaluated the clinical outcome of the disease in the absence of adequate therapy, as well as in the course of natural development [8].

The causal relationship between prognostic factors and the risk for developing lymphoma should not be based on data from retrospective studies, but primarily on prospective studies. It has been shown that the number of prognostic factors for developing lymphoma in primary Sjögren's syndrome is sufficiently large [9].

Table 1. Prognostic factors and the risk for developing lymphomas

Prognostic factors	Number of tests (N)		Significance of odds ratios	
	Increased risk	No difference	Minimum significance	Maximum significance
Age at the time of diagnosis	1	4	-	-
Male gender	7	2	1.58	28.73
Enlarged parotid glands	11	1	2.84	15.10
Dry mouth	0	4	-	-
Dry keratoconjunctivitis	0	3	-	-
Arthralgia	0	2	-	-
Splenomegaly	5	1	3.97	19.90
Lymphadenopathy	7	0	2.62	9.70
Skin purpura / vasculitis	6	1	3.30	16.30
Systemic activity	5	0	1.07	2.56

Table 2. Laboratory tests and the risk for developing lymphomas

Prognostic factors	Number of tests (N)		Significance of odds ratios	
	Increased risk	No difference	Minimum significance	Maximum significance
Gammopathy ↑ IgG	2	1	2.54	4.06
CD4/CD8 < 0.8	3	0	-	10.92
↑ β2-microglobulin	2	0	-	1.90
Anemia	2	1	0.89	3.43
Leukopenia	3	1	0.51	3.43
Lymphopenia	3	2	2.12	8.70
Neutropenia	1	1	1.24	16.47
ANA	0	4	1.15	8.97
RF	3	4	0.94	2.56
Anti-Ro/La	3	4	0.66	3.50
↓ C4	15	2	1.76	4.50
↓ C3	6	2	3.25	39.70
Cryoglobulinemia	10	2	1.9	7.66
Monoclonal IgG	3	1	1.3	22.30
Focus score	2	1	1.84	5.70
Atypical germinal centers	1	2	5	5.80

EPIDEMIOLOGICAL FACTORS AND RISK FOR DEVELOPING LYMPHOMAS

Age plays a key role in the diagnosis of primary Sjögren's syndrome. It has been found that when the disease is diagnosed at young age, lymphomas develop more frequently. These data are not supported by other authors. Age remains a controversial factor, depending on the type of studies – retrospective or prospective. [9]

Regarding the role of gender in the development of lymphomas, it has been shown that in male compared to female patients, lymphomas develop earlier and more frequently in the course of the disease – the incidence rate is from 3 to 28 times higher in men. This is also in support of the data for other hemoblastoses: the incidence rate of myeloma (43:36) and Hodgkin's disease (59:16) is higher in men than women, and the risk for developing non-Hodgkin's lymphoma in men is 18 versus 5 times increased risk in women.

Regarding the role of clinical markers as a risk factor for the development of lymphomas in patients with primary Sjögren's syndrome, data continue to be added.

Despite the painful „sicca syndrome“, it has been found that its severity does not correlate with the risk for developing lymphomas. The systemic activity of the disease and organ involvement correlates, however, with the EULAR ESSDAI scale (EULAR

Sjögren's Syndrome Disease Activity Index) – an index for determining disease activity in primary Sjögren's syndrome [10].

The involvement of glandular structures and specifically parotid salivary glands determines a very high risk for developing lymphomas. In 2/3 of the cases, lymphomas arise in the parotid glands (MALT lymphomas).

Regarding the presence of lymphadenomegaly, its role has been proven, in parallel with the presence of splenomegaly. Enlarged lymph nodes and an enlarged spleen are recorded for a varying length of time before lymphoma proliferation. For the lymphomas different from MALT, the appearance of a generalized enlargement of lymph nodes is characteristic [11].

Skin involvement is usually associated with the development of systemic vasculitis, and lymphoma infiltrates in the skin are much less frequently demonstrated. Cryoglobulinemia and cryoglobulinemic type of vasculitis are frequently found. The degree of clinical manifestation of vasculitis also depends on the caliber of the affected vessels.

According to the ESSDAI scale, the presence of cutaneous vasculitis defines a moderate or severe type of primary Sjögren's syndrome activity. The appearance of skin purpura with or without ulcers is a key prognostic marker for the development of lymphomas.

Hypergammaglobulinemic purpura is associated with polyclonal B-cell activity and has a better prognosis [10, 12, 13, 14].

Laboratory markers and the risk for developing lymphomas in patients with primary Sjögren's syndrome include: B-cell polyclonal hyperactivity, increased level of β 2-microglobulin, presence of leukopenia as a sensitive laboratory marker. The combination of leukopenia with lymphopenia also marks an increased risk for the development of lymphomas [9].

IMMUNOLOGICAL MARKERS AS PREDICTORS OF LYMPHOMA DEVELOPMENT IN PRIMARY SJÖGREN'S SYNDROME

According to literature data, autoantibodies pose controversial questions and answers, largely determined by the study design. The role of Ro/SS-A and La/SS-B autoantibodies has been part of this long-standing controversy. In addition, no study has identified elevated ANA as a marker for lymphoma development. In 2016, a case-control study design demonstrated that Ro/SS-A and La/SS-B autoantibodies are independent predictors for developing non-Hodgkin's lymphomas in patients with primary Sjögren's syndrome. The studies in Sweden, Spain and Norway have not found, however, an association between the risk of lymphoma and the titers of Ro and La autoantibodies [15, 16, 17].

Cryoglobulins increase their importance as a risk factor if they are associated with other abnormali-

ties, such as increased levels of rheumatoid factors, reduced C3 and C4 fractions of the complement. Monoclonal serum immunoglobulins are considered the strongest predictors of lymphoma development in patients with primary Sjögren's syndrome ($p < 0.0001$) [18].

Cryoglobulinemia correlates with the ESSDAI activity and severity scale as a risk factor for lymphoma development, associated with lymph node enlargement, glandular organ involvement, and hematologic abnormalities.

Decreased C3 and C4 fractions of the complement correlate with both the risk of lymphoma development and increased mortality. C4 has been found to show a stronger correlation with the risk for developing lymphoma [18, 19].

PRACTICAL APPROACH AND RECOMMENDATIONS

Non-Hodgkin's lymphomas (NHLs) in patients with autoimmune systemic diseases have different characteristics compared to NHLs in persons without autoimmune diseases [20, 21, 22]:

- The frequency of extranodular involvement is increased (87% of patients)
- There is an association between the ANA titer and extraglandular manifestations of lymphoma
- The role of prior corticosteroid therapy in relation to the severity of lymphoma involvement and progression has been demonstrated [23, 24, 25].

Table 3. Role of individual prognostic factors for the development of lymphomas in primary Sjögren's syndrome

	Prognostic factor	Degree of significance
Very strong	Low C4 levels	15
	Enlarged parotid glands	11
	Cryoglobulinemia	10
Strong	Lymphadenopathy	7
	Male gender	7
	Skin purpura/vasculitis	6
	Low C3 levels	6
	Splenomegaly	5
	Systemic activity	5
Weak	CD4/CD8 < 0.8	3
	Low CH 50 levels	3
	Leukopenia	3
	Hypergammaglobulinemia	3

Table 4. Prognostic factors and strength of their degree of significance

	Prognostic factor	Degree of significance
Weak	Rheumatoid factor	3
	Anti-Ro/La	3
	$\uparrow$ β 2-microglobulin	2
	$\uparrow$ IgG	2
	Anemia	2
Unclear	Germinative centers	1
	Neutropenia	1
	Focus score	1
	Age at the time of diagnosis	1
	Arthralgia	0
	Dry keratoconjunctivitis	0
	Dry mouth	0
	ANA	0

The clinical picture of the primary Sjögren's syndrome in the case of lymphoma development is diverse, due to the following impacts [26, 27, 28]:

1. A significant number of prognostic factors
2. Characteristic histological maps and Focus score
3. Role of previous therapy for the underlying disease.

A synergistic model of prognostic factors was created in 2016, which determines that:

1. In the presence of at least three risk factors, there is an increase of up to 40% in the risk of non-Hodgkin's lymphoma
2. In the presence of seven risk factors, the risk reaches 100%
3. In patients with primary Sjögren's syndrome and the presence of three risk factors, the risk for developing lymphoma increases 30 times compared to healthy persons [13].

Non-Hodgkin's lymphomas include different biological and clinical subtypes, which are associated with the activity of primary Sjögren's syndrome, concomitant HCV infection, familial history of blast leukemia, myeloma, smoking, alcohol abuse.

Drug treatment and the risk for developing lymphomas in patients with primary Sjögren's syndrome is related to the activity of the autoimmune disease itself, the processes of lymphomagenesis, and the side effects of immunosuppressive and biological therapy [14, 29, 30].

Modern anti-B-cell therapy, with the expected benefits regarding disease activity, could potentially prevent the development of lymphomas, thus providing certain control over malignant lymphoproliferation [14].

THE RISK FOR DEVELOPING LYMPHOMAS IN THE SECONDARY FORMS OF THE DISEASE

Secondary Sjögren's syndrome can develop in the course of other autoimmune diseases, such as rheumatoid arthritis, progressive systemic sclerosis, systemic lupus erythematosus, vasculitis, antiphospholipid syndrome, organ-specific autoimmune diseases – Hashimoto's thyroiditis, primary biliary cirrhosis, autoimmune hepatitis [19, 31].

Despite conflicting data from the literature, the opinion has been accepted that the risk for developing lymphomas in primary Sjögren's syndrome is significantly higher than that in the secondary forms of the disease. In secondary Sjögren's syndrome,

leading factors are the degree of activity, systemic involvement and therapy of the underlying disease.

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