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CASE REPORT

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# Primary Sjögren's syndrome complicated by development of B-cell lymphoma

## ABSTRACT

Sjögren's syndrome is a chronic autoimmune inflammatory connective tissue disease of unknown aetiology. It is marked by lymphocytic infiltration of exocrine glands (mainly lacrimal glands and salivary glands), which impairs their function and leads, among other things, to symptoms of dryness that are typical of this syndrome. In addition to glandular lesions, other organs and systems such as the gastrointestinal tract, nervous system and vasculitis may also be involved. There is also a significantly higher incidence of lymphomas in primary Sjögren's syndrome compared to the general population. This paper presents a case report of a 63-year-old female patient with primary Sjögren's syndrome who presented with a worsening of her condition and the development of B-cell lymphoma in the course of her disease.

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**Key words: Sjögren's syndrome; lymphoma; salivary gland enlargement; salivary gland biopsy**

## INTRODUCTION

Sjögren's syndrome is a chronic autoimmune inflammatory connective tissue disease of unknown aetiology. It is marked by the formation of lymphocytic infiltrates in tissues of exocrine glands (usually the lacrimal glands, salivary glands and pancreas). This process leads to impairment of their function and inflammatory changes in other systems and organs, i.e. the musculoskeletal system, urinary tract and kidneys, gastrointestinal tract, thyroid or reproductive organs, as well as extraglandular lesions, i.e. vasculitis, central and peripheral nervous system involvement or interstitial lung disease [1, 2].

Sjögren's syndrome may be primary (idiopathic) or secondary — occurring in the course of other diseases, including rheumatologic diseases such as rheumatoid arthritis or systemic lupus.

The first symptom that accompanies this disease is dry eyes, dry mouth or dry genitals, which is reflected in the classification criteria. This is a consequence of the inflammatory process in the secretory glands, leading to a decrease in the amount of secretion, as well as changes in its composition [1]. The underlying pathogenesis of the disease is epithelial damage, release of autoantigens, stimulation of the immune response leading to B-lymphocyte hyperreactivity, production of autoantibodies (anti-SSA/Ro, anti-SSB/La), and polyclonal hypergammaglobulinemia [2].

The disease can present diagnostic difficulties. Complaints involving multiple organs systems often result in patients being referred to various specialists, and initial symptoms are not immediately associated clearly with the rheumatologic disorder that is Sjögren's syndrome. Its early diagnosis is of great importance because of the risk of developing lymphomas that often accompany the syndrome [3].

The aetiology of the syndrome is unknown. The likely origin may be genetic. There was an association of symptoms with the presence of tissue compatibility antigens (HLA, human leukocyte antigen): HLA-B8, -Dw3, -DR, -w52, -DQ [2, 4]. It is also possible

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to observe the phenomenon of gene polymorphisms contributing to lymphoma formation in the course of this syndrome [3, 4]. Estrogen deficiency, environmental factors, viral infections such as hepatitis C virus (HCV), human immunodeficiency virus (HIV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV) infections may be partly responsible for the development of the disease [5–7].

Inflammatory infiltrates occur in the exocrine glands and some other organs, involving T cells, B cells and plasma cells, among others. The smouldering signs of inflammation continually lead to impaired secretory function of the organs. B lymphocytes are further stimulated by cytokines such as interleukins (IL): IL-6, IL-21, IL-24, and others. As a result, there may be excessive proliferation, including monoclonal proliferation. This is also accompanied by the production of autoantibodies, e.g. antibodies against cytoplasmic antigens of ribonucleins (SSA) and antibodies against soluble ribonucleoprotein antigens that are sensitive to ribonuclease and trypsin (SSB), rheumatoid factor (RF), anti-centromere antibodies (ACA), anti-cardiolipin antibodies (APLA) [8, 9].

Results from a 2005 Swedish study indicate a 16-fold increased risk of lymphoma in patients diagnosed with Sjögren's syndrome compared to the general population [10]. The risk of developing cancer increases with the duration of the disease. B-cell marginal zone lymphomas develop most commonly in primary Sjögren's syndrome. Regulatory T lymphocytes, which inhibit the activity of polyclonal T-cell infiltrates at sites of inflammation, play a major role in the neoplastic transformation, improving the survival of B-cell clones [11]. T lymphocytes, through the production of factors that activate B-cell proliferation, can promote the development of lymphomas [11].

## CASE REPORT

A 63-year-old female patient was admitted to the Rheumatology Department of the Regional Polyclinical Hospital in Elbląg for diagnostic investigations in November 2016. For two years, the patient had the following symptoms: dry eyes and dry mouth, a sensation of having a particle of sand under her eyelids, chronic dry cough and symptoms of gastroesophageal reflux disease. The patient was under the care of an oncology outpatient clinic. In the past, four years prior to hospitalisation, she had a complete removal of her organ of reproduction and had undergone a single 18-hour brachytherapy for endometrial cancer. A complete remission of the disease was achieved. In addition, the patient had a positive history of hypertension and diabetes treated with oral antidiabetic drugs.

In July 2016, the patient noticed enlargement of the parotid glands (more on the right than on the left) and the upper, middle and lower cervical lymph nodes. She initially reported to the oncology outpatient clinic. An ultrasound (US) examination of the salivary glands and a biopsy of the right parotid gland were performed. The histopathological examination revealed lymphocytic infiltration of the salivary gland parenchyma suggestive of Sjögren's syndrome. An ENT consultation was also conducted and the patient was eventually referred to the rheumatology outpatient clinic, where she was admitted at the end of October 2016. From there, she was subsequently referred to the rheumatology department to complete the diagnostic process (November 2016).

The patient was admitted to the department in general good condition. On physical examination, abnormalities included enlargement of parotid glands (more on the right than on the left) and upper, middle and lower cervical lymph nodes.

Extensive laboratory and imaging tests were performed in the rheumatology department. The patient's laboratory abnormalities are shown in Table 1. In addition, salivary gland ultrasound and right salivary gland biopsy were previously performed on an outpatient basis within the outpatient oncology clinic. The histopathological examination showed lymphocytic infiltration of the salivary gland parenchyma suggestive of Sjögren's syndrome. Other laboratory and imaging findings were normal.

The patient underwent an ophthalmology consultation and a Schirmer's test was performed, which was positive (right eye 5 mm, left eye 5 mm). The ophthalmologist clearly identified abnormal tear secretion.

In view of the awareness of the significant risk of lymphoma in patients diagnosed with Sjögren's syndrome, taking also into account the patient's lymphadenopathy, it was decided to consult an oncological surgeon and that a cervical lymph node should be taken for histopathological examination. Based on the histopathological result obtained, a marginal zone B-cell lymphoma was diagnosed.

**Table 1.** Laboratory abnormalities of the examined patient

| Parameter | Value |
|---|---|
| RF | 363 IU/ml |
| D-dimers | 704 ng/ml |
| ESR | 53 mm/h |
| EBV IgG antibodies | Positive result |
| CMV IgG antibodies | Positive result |
| Toxoplasmosis IgG antibodies | Positive result |
| Vitamin D3 levels | 18.2 ng/ml |
| Polyclonal hypergammaglobulinemia | 25% |
| ANA-HEp2 antibodies | Titre 1:2560, SSA (3+) and SSB (+) antibodies present in the immunoblot profile |

RF — rheumatoid factor; ESR — erythrocyte sedimentation rate; EBV — Epstein-Barr virus; CMV — cytomegalovirus; ANA — antinuclear antibodies; SSA — antibodies against cytoplasmic antigens of ribonucleins; SSB — antibodies against soluble ribonucleoprotein antigens that are sensitive to ribonuclease and trypsin

Immunohistochemistry: CD 20(+), CD 3(–), CD43(+), CD5(+), bcl2(+), cyclin D1(–), bcl6(–), CD10(–), CD21(–), CD23(–), Ki-67 index of approximately 40%.

After discharge from the rheumatology department, the patient was referred to the oncology outpatient clinic for further treatment. She was finally approved for local treatment with radical teleradiotherapy (linear accelerator, 6 MV photons, intensity-modulated radiation therapy (IMRT) to the cervical, supraclavicular and axillary regions bilaterally, Dg = 24 Gy/12 fractions).

After the administered treatment, complete remission of the oncohematological disease was achieved. There has been no relapse in the patient's condition to date. The patient has been under observation for over 6 years now and only needs regular medical check-ups.

## DISCUSSION

Sjögren's syndrome is a chronic autoimmune inflammatory disease of the exocrine glands, impairing the function of many organs, in the course of which lymphomas may also develop [3].

Women are more commonly affected than men (9:1). The peak incidence is in the fourth and fifth decades of life. The main component of the inflammatory infiltrate of the organs involved are T lymphocytes, accompanied by B lymphocytes that are responsible for antibody production. It is likely that viral infections may have an initiating effect on the inflammatory process [7, 12, 13]. The patient showed positive EBV IgG antibodies, CMV IgG antibodies and toxoplasmosis IgG antibodies.

The primary clinical manifestation in this syndrome is dryness of the mucous membranes of the mouth, throat and eyes. Sjögren's syndrome develops insidiously and slowly — in the case described above, complaints have been present for 2 years — and its diagnosis is often delayed [1, 2].

The most common symptoms reported by patients include dry eyes, a sensation of having a particle of sand under the eyelids, keratitis, dry mouth, dental lesions with increased caries, enlargement of the salivary glands and lymph nodes, problems with swallowing and digestion, gastroesophageal reflux disease, skin lesions, muscle and joint pain, arthralgia and arthritis, generalised symptoms: subfebrile states, fatigue. In addition, Sjögren's syndrome may be accompanied by polyneuropathy, autoimmune thyroiditis, Raynaud's phenomenon, vasculitis, liver and kidney dysfunction, cranial nerve involvement, complete blood count changes such as anaemia, leukopenia, thrombocytopenia, polyclonal gammopathy, positive RF, accelerated erythrocyte sedimentation rate (ESR), presence of elevated titres of SSA and SSB antibodies. Slow destruction of the exocrine glands can also cause dryness of the upper respiratory tract, chronic dry cough, autoimmune pancreatitis, and vaginal dryness [4, 14].

Most of the listed symptoms and complaints were reported by the patient. Similarly, accelerated ESR, presence of positive RF, positive antibodies in a significant titer of 1:2560 — SSA and SSB, polyclonal gammopathy were observed in laboratory tests. Physical examination revealed enlarged cervical lymph nodes and enlarged salivary glands. The histopathological examination of the salivary gland biopsy revealed a typical pattern for Sjögren's syndrome.

It is worth emphasising that the diagnotic work-up for the disease uses both laboratory, radiological and histopathological tests, which complement each other, leading to a correct diagnosis of rheumatological disease based on the 2016 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria [15, 16].

It should be noted that the differential diagnosis also needs to take into account oth-

er diseases that cause dry mouth, medications that can cause dryness and diseases associated with salivary gland enlargement: inflammation, bacterial infections, primary tumours, sialolithiasis, EBV infection, CMV infection, mumps virus infection, tuberculosis, alcoholism, liver cirrhosis, anorexia [15, 16], which was taken into account during hospitalisation.

In addition, fibromyalgia, age-related changes, neurological disorders, endocrine disorders resulting in less frequent blinking, lacrimal gland dysfunction, diabetes, hypercalcaemia, IgG4-related systemic disease, and psychogenic factors should be considered in the differential diagnosis. When signs of arthritis are present, secondary Sjögren's syndrome should be considered, e.g. in the course of rheumatoid arthritis.

After a thorough analysis of the laboratory, immunological, histopathological and imaging tests performed, and considering the patient's clinical condition, Sjögren's syndrome was clearly diagnosed based on qualifying criteria.

As Sjögren's syndrome also has a significantly higher incidence of lymphomas compared to the general population, this should increase the clinician's vigilance [3, 17, 18].

Most lymphomas are of the MALT (mucosa-associated lymphoid tissue) type. They usually have a slow course and approximately 90% of patients survive for five years. Neoplastic transformation can occur in a variety of organs, not only in the sites originally involved in the lymphoproliferative process (parotid glands and lacrimal glands) [20]. Factors that increase the risk of lymphoma include chronic parotid gland enlargement, lymphadenopathy, polyclonal gammopathy (i.e. in the patient described), as well as polyneuropathy, splenomegaly, peliosis, and vasculitis [21]. Therefore, a histopathological examination of the enlarged neck lymph node was considered necessary in this case.

The patient also had a history of infections of EBV and CMV aetiology, which is an additional adverse factor in the development of the oncohematological process. Indeed, infectious agents may also independently influence lymphoma formation through direct tropism towards lymphocytes, leading to their neoplastic transformation, induction of immunosuppression or through chronic stimulation of the immune system [22, 23].

Comprehensive rheumatological, radiological, ophthalmological and pathomorphological diagnostic methods made it possible not only to make a clear diagnosis but also to apply appropriate treatment, including oncology treatment.

## CONCLUSIONS

The risk of oncological disease in patients diagnosed with Sjögren's syndrome, such as lymphomas, increases with duration of the disease [13, 14]. Therefore, oncological vigilance, appropriate rheumatology monitoring, and correct diagnosis are important, especially in patients with risk factors for their development and after viral infections, which significantly affects prognosis and the course of treatment. It is important to emphasise the necessity of an interdisciplinary approach to patients with rheumatologic diseases. These patients have a greater predisposition to oncological diseases, which should always increase the vigilance of any experienced rheumatology clinician.

### ETHICS STATEMENT

Patient consent was obtained for publication of the case.

### AUTHOR CONTRIBUTIONS

M.R. — writing the article concerning the case report of the clinically managed patient, M.K. — substantive supervision

### CONFLICT OF INTEREST

The authors report no conflict of interest.


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## References


1. Maślińska M, Przygodzka M, Kwiatkowska B, et al. Sjögren's syndrome: still not fully understood disease. Rheumatol Int. 2015; 35(2): 233–241, doi: 10.1007/s00296-014-3072-5, indexed in Pubmed: 24985362.
2. Bombardieri M, Argyropoulou OD, Ferro F, et al. One year in review 2020: pathogenesis of primary Sjögren's syndrome. Clin Exp Rheumatol. 2020; 38 Suppl 126(4): 3–9, indexed in Pubmed: 33025887.
3. Nocturne G, Virone A, Ng WF, et al. Rheumatoid Factor and Disease Activity Are Independent Predictors of Lymphoma in Primary Sjögren's Syndrome. Arthritis Rheumatol. 2016; 68(4): 977–985, doi: 10.1002/art.39518, indexed in Pubmed: 26606524.
4. Shimizu T, Nakamura H, Kawakami A. Role of the Innate Immunity Signaling Pathway in the Pathogenesis of Sjögren's Syndrome. Int J Mol Sci. 2021;

22(6), doi: 10.3390/ijms22063090, indexed in Pubmed: 33803026.
5. Delaleu N, Jonsson R, Koller MM. Sjögren's syndrome. Eur J Oral Sci. 2005; 113(2): 101–113, doi: 10.1111/j.1600-0722.2004.00183.x, indexed in Pubmed: 15819815.
6. Madaliński K, Dzierzanowska-Fangrat K, Jóźwiak P, et al. Rola zakażeń wirusem zapalenia wątroby typu C w patogenezie zespołu Sjögrena. Pol Arch Med Wewn. 2002; 107(2): 167–171, indexed in Pubmed: 12107973.
7. Lendrem D, Mitchell S, McMeekin P, et al. UK primary Sjögren's Syndrome Registry. Health-related utility values of patients with primary Sjögren's syndrome and its predictors. Ann Rheum Dis. 2014; 73(7): 1362–1368, doi: 10.1136/annrheumdis-2012-202863, indexed in Pubmed: 23761688.
8. Skopouli FN, Dafni U, Ioannidis JP, et al. Clinical evolution, and morbidity and mortality of primary Sjögren's syndrome. Semin Arthritis Rheum. 2000; 29(5): 296–304, doi: 10.1016/s0049-0172(00)80016-5, indexed in Pubmed: 10805354.
9. Chivasso C, Sarrand J, Perret J, et al. The Involvement of Innate and Adaptive Immunity in the Initiation and Perpetuation of Sjögren's Syndrome. Int J Mol Sci. 2021; 22(2), doi: 10.3390/ijms22020658, indexed in Pubmed: 33440862.
10. Theander E, Henriksson G, Ljungberg O, et al. Lymphoma and other malignancies in primary Sjögren's syndrome: a cohort study on cancer incidence and lymphoma predictors. Ann Rheum Dis. 2006; 65(6): 796–803, doi: 10.1136/ard.2005.041186, indexed in Pubmed: 16284097.
11. Gottenberg JE, Lavie F, Abbed K, et al. CD4 CD25high regulatory T cells are not impaired in patients with primary Sjögren's syndrome. J Autoimmun. 2005; 24(3): 235–242, doi: 10.1016/j.jaut.2005.01.015, indexed in Pubmed: 15848046.
12. Fox RI, Luppi M, Kang HI, et al. Detection of Epstein-Barr virus-associated antigens and DNA in salivary gland biopsies from patients with Sjogren's syndrome. J Immunol. 1986; 137(10): 3162–3168, indexed in Pubmed: 3021847.
13. Wen S, Shimizu N, Yoshiyama H, et al. Association of Epstein-Barr virus (EBV) with Sjögren's syndrome: differential EBV expression between epithelial cells and lymphocytes in salivary glands. Am J Pathol. 1996; 149(5): 1511–1517, indexed in Pubmed: 8909241.
14. Ramos-Casals M, Brito-Zerón P, Font J. The overlap of Sjögren's syndrome with other systemic autoimmune diseases. Semin Arthritis Rheum. 2007; 36(4): 246–255, doi: 10.1016/j.semarthrit.2006.08.007, indexed in Pubmed: 16996579.
15. Rasmussen A, Ice JA, Li He, et al. Comparison of the American-European Consensus Group Sjogren's syndrome classification criteria to newly proposed American College of Rheumatology criteria in a large, carefully characterised sicca cohort. Ann Rheum Dis. 2014; 73(1): 31–38, doi: 10.1136/annrheumdis-2013-203845, indexed in Pubmed: 23968620.
16. Shiboski CH, Shiboski SC, Seror R, et al. International Sjögren's Syndrome Criteria Working Group. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis Rheumatol. 2017; 69(1): 35–45, doi: 10.1002/art.39859, indexed in Pubmed: 27785888.
17. Nocturne G, Mariette X. Sjögren Syndrome-associated lymphomas: an update on pathogenesis and management. Br J Haematol. 2015; 168(3): 317–327, doi: 10.1111/bjh.13192, indexed in Pubmed: 25316606.
18. Alunno A, Leone MC, Giacomelli R, et al. Lymphoma and Lymphomagenesis in Primary Sjögren's Syndrome. Front Med (Lausanne). 2018; 5: 102, doi: 10.3389/fmed.2018.00102, indexed in Pubmed: 29707540.
19. Świerkocka K, Łącki JK. Chłoniaki w zespole Sjögrena. Reumatologia. 2008; 46: 16–20.
20. Theander E, Vasaitis L, Baecklund E, et al. Lymphoid organisation in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjögren's syndrome. Ann Rheum Dis. 2011; 70(8): 1363–1368, doi: 10.1136/ard.2010.144782, indexed in Pubmed: 21715359.
21. Ioannidis JPA, Vassiliou VA, Moutsopoulos HM. Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjögren's syndrome. Arthritis Rheum. 2002; 46(3): 741–747, doi: 10.1002/art.10221, indexed in Pubmed: 11920410.
22. Gasparotto D, De Vita S, De Re V, et al. Extrasalivary lymphoma development in Sjögren's syndrome: clonal evolution from parotid gland lymphoproliferation and role of local triggering. Arthritis Rheum. 2003; 48(11): 3181–3186, doi: 10.1002/art.11286, indexed in Pubmed: 14613281.
23. Manganelli P, Fietta P, Quaini F. Hematologic manifestations of primary Sjögren's syndrome. Clin Exp Rheumatol. 2006; 24(4): 438–448, indexed in Pubmed: 16956437.