**Diffuse Large B-Cell Lymphoma as a Sequela of Sjögren’s Syndrome: A Case Report**

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Abstract: We present a case of a 45-year-old woman with primary Sjögren’s syndrome, who in 2005, one year after the onset of the systemic autoimmune disease developed chronic lymphocytic leukaemia, which eventually transformed - denoted as Richter’s transformation - into diffuse large B-cell lymphoma in 2006. She had recurrent lymphadenopathy on the neck region from 2002. In September 2005 anaemia and elevated LDH enzyme levels were detected with persistent subfebrility and lymphatic node enlargement on her neck and axillary region. Chest and abdominal CT, biopsy from the lymphoid glands and crista biopsy were performed and B-CLL was diagnosed, therefore chlorambucil treatment was administered. After two cycles of chlorambucil the pulmonary involvement extended, the patient had high fever and the abdominal CT showed the appearance of multiple hypodens lesions in the liver. Based on the histological evaluation of the hypodens lesions of the liver, the diagnosis of diffuse large B-cell lymphoma has been established, therefore 8 cycles of R-CHOP treatment were administered. The patient has been in complete remission since then.

Conclusion: The main message of this case report is that lymphadenopathy, the decrease of serum immunoglobulin levels and autoantibody titres, as well as the predominance of monoclonal gammopathy point to the possibility of malignant transformation in patients with Sjögren’s syndrome.

**INTRODUCTION**

The frequent association between autoimmune diseases and non-Hodgkin’s lymphoma (NHL) has been described previously and could be explained - at least partially – that the immunoproliferative disorders in these patients are probably multi-causal (genetic predisposition, toxic immunosuppressant therapies). Sjögren’s syndrome (SS) is associated with an increased risk of NHL (4- to 40-fold and higher risk for primary disease than for secondary disease). A 1000-fold increased risk of parotid gland marginal zone lymphoma, diffuse large B-cell and follicular lymphomas have been described [1-3]. NHL is considered to be the most serious complication of SS. The risk of developing NHL, which is equivalent to both primary and secondary SS, is estimated to be 44 times higher than that of in a healthy population [3]. NHLs in SS patients occur chiefly in salivary glands and in other mucosa-associated lymphoid tissues (MALT), as well as in lymph nodes and bone marrow. The evolution from benign lymphocytic infiltration characteristic of SS to malignant NHL is probably a multi-step process. However, the underlying molecular events are still unknown [4-8]. Although the exact pathomechanism is unknown, there are clinical predisposing factors for the occurrence of NHL in SS patients such as parotid gland’s enlargement, splenomegaly, lymphadenopathy, palpable purpura and laboratory parameters (e.g. presence of low levels of complements, mixed cryoglobulinemia, decrease in serum polyclonal immunoglobulins, or the presence of serum or urinary monoclonal components) [1-8]. In SS each subtype of NHLs has been reported, the most common types of them are the extra-nodal B-cell type mucosa-associated lymphoid tissue (MALT) lymphomas (28-fold increased risk compared to the normal population) and the aggressive diffuse large B-cell lymphomas (11-fold increased risk compared to the normal population). Thus, the association between SS and MALT lymphomas is well-defined and known, we believe that in SS, diffuse large B-cell lymphomas should get more attention because of their frequent occurrence in this systemic autoimmune disease. However, the common features of their pathomechanisms still need to be explored. [9-12]. The main elements of common pathomechanism between SS and NHLs are the following: chronic antigen stimulation in the exocrine glands, high level of B-cell activating factor (BAFF), major genetic aberrations which may lead to failure in the apoptotic system, which generally leads to uncontrolled proliferation [9-14]. Richter’s syndrome is the transformation of a chronic lymphocytic leukaemia (CLL) into a diffuse large B-cell lymphoma. This evolution is an unusual and serious complication of CLL with an incidence of 1-10% of all CLL cases [15]. CLL and the diffuse large B-cell lymphoma (DLBCL) are very different forms of malignant lymphoproliferative diseases with different aggressiveness, morphological characteristics and surface markers such as many types of clusters of differentiation molecules (CDs) for example CD5, CD19, CD23 in B-CLL and CD20 in DLBCL [15].

According to our best knowledge there is no example or case-report which explains the association between Sjögren’s and Richter’s syndrome. The main aim of this work is to...
examine this very rare type association of NHL lymphomas to SS while showing its clinical characteristic and special laboratory findings of this association.

CASE DESCRIPTION

In 2002 a 39-year old female accountant attended our clinic with persistent lymphadenomegaly on her neck region. Two biopsies from the lymph node conglomerate were performed between 2002 and 2004. Without evidence of malignancy, the histological evaluation showed immunoreactive diffuse hyperplasy. The patient had no family history of malignancy or autoimmune disorders. In her past medical history there were no significant illnesses before 2002. After 2002 the patient attended our out-patient clinic for control every three months and other symptoms (xerophthalmy, xerostomy, vasculitis with palpable purpura) gradually developed which suggested the onset of a systemic autoimmune disease. In our out-patient clinic there is a general practice that we check our patients every 6 months to observe the changes of symptoms or laboratory parameters of systemic autoimmune disease. Those cases where any dysfunctions suggesting manifestation of lymphoproliferative disorders had been found are checked every 3 months. Positive laboratory findings were: rheumatoid factor (RF)-, anti-beta2 glykoproteins (IgG-, IgM) and anti-cardiolipin (CL IgG-, A-, M isotypes too) autoantibody positivity, low level of complements (C4, C1q) and reduced (0.06 ml/min) saliva production with sialometry. The patient had objective xerostomy and xerophthalmy with positive results of diagnostic tests such as Schirmer’s-test and sialometry; she had elevated levels of anti-SS-A and anti-SS-B, and minor salivary gland biopsy was performed to fulfil the histological diagnostic criteria for SS. Finally, the patient fulfilled the diagnostic criteria for primary SS according to the corresponding diagnostic criteria in February 2005 [16]. In September 2005, according to present classification system, RAI3 stage of B-CLL was diagnosed with lymphocytosis, lymphatic node enlargement, splenomegaly and anaemia, therefore chlorambucil treatment was administered. During the next check-up in March 2006, we repeated the chest CT and we found that the diameter of the consolidation increased (from 6 to 8 cms) and this solid structure transformed to a multilocular-cystic lesion and new small (1-1.5 cm) round shadows appeared in the upper lobes of the right and left lungs (Figs. 2, 3). After 2 cycles of chlorambucil the pulmonary involvement extended. The repeated abdominal CT showed multiple, hypodens lesions in the liver and besides the known lymph node enlargement in the retroperitoneal region, new abnormal lymph nodes appeared along the great vessels (aorta and celiac trunc) of the abdomen and in the hile of the liver. In March 2006 we found 80 g/L hypochrom, microcyter anaemia (mean cell volume

Fig. (1). The biopsy from the axillary lymph node suggested small lymphocytic lymphoma (anti-CD5 staining, 20x).
The association of NHL with SS has been described in detail previously [1-12] although the underlying pathogenic background is still unknown. Richter’s syndrome denotes the development of aggressive lymphoma that arises in patients with CLL. Richter’s transformation is a very rare entity which occurs in approximately 1-10% of CLL patients. Treatment options for these patients are limited and include combination chemotherapy with or without the addition of monoclonal antibodies and stem cell transplantation [17, 18]. In this work we showed an important case of this rare syndrome, with a positive outcome. To the best of our knowledge the association between Richter’s syndrome and SS has not been described previously. The pathogenesis of NHL in SS is an intricate multi-step process, including B cell monoclonal proliferation, driven by oncogenic and/or infectious agents, as well as cytokines. Various predictive factors such as persistent enlargement of parotid glands, adenopathy, splenomegaly, palpable purpura, low levels of various complements, mixed cryoglobulinemia, monoclonal gammopathy, and decrease in serum polyclonal immunoglobulins suggest potential lymphoma evolution [1-8]. Several genetic aberrations of MALT lymphoma have been identified, some of which appear to play an important role in the pathogenesis of the disease. For example the mutation of MALT1 gene with translocation mechanism t(11;18)(q21;q21) is considered to be specific for MALT lymphomas. This translocation results in the synthesis of the API2-MALT1 fusion protein, which can activate nuclear factor-KB, a transcription factor for a number of survival-related genes. Up-regulation of these molecules promotes cellular proliferation and resistance to apoptotic signals. Another translocation of t(14;18)(q32;q21) involving IGH and MALT1 in patients with MALT lymphomas has been reported, too. Although the potential function of this particular translocation in the pathogenesis of MALT lymphomas has not yet been elucidated, these findings together with the data published on t(11;18)(q21;q21) suggest MALT1 rearrangements in up to 50% of all patients with MALT lymphoma. The NHLs in SS are usually B-cell neoplasms in which the clonally rearrangements of the im-

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![Fig. (2)](image1.png) The chest X-ray showing multiple round shadows perihilar and a large consolidation with necrotic parts (the diameter of this consolidation was 60 mm) in the heart-diaphragm square.

![Fig. (3)](image2.png) The solid structure of the lesion in the heart-diaphragm square subsequently transformed to a multilocular-cystic lesion and new small (1-1.5 cm) round shadows appeared in the right and left upper lobes of the lungs in March 2006 (chest CT).
munoglobulin genes have been found. Recently data suggest that certain mutations in the genes of Fas (one of the cell-surface receptors involved in cell death pathway) and Fas ligand (Fas-L) can play important role in the pathogenesis of autoimmune-related lymphoproliferation. As stated in other findings the expression of Bcl-2 (one of the anti-apoptotic proteins) and the relative decrease of Bax (with pro-apoptotic effect) together with an increasing Bcl-2/Bax ratio in cells may explain their resistance to apoptosis, resulting in a prolonged life-span and the perpetuation of conditions which may lead to the development of lymphomas [19-24]. The common genetic background of the association of SS and Richter’s syndrome has not been described previously in the literature. SS can associate with any type of NHL. Its association with DLBCL has been found to become more frequent. In this report we described a severe case with the second most frequent type of NHL in SS, fortunately with a favourable outcome owing to modern chemotherapy. The treatment of SS associated NHL depends on the type of the lymphoma itself. Rituximab has been used in the treatment of NHL since 1997. The first observations on the additional therapy using monoclonal antibodies in DLBCL were published by Coiffier et al. in 2002 and they reported better remission rate with rituximab opposed to CHOP combination alone [25]. Further successful treatments in DLBCL with added rituximab therapy have been described previously [26-29]. The exact mode of action of rituximab (anti-CD20 monoclonal antibody) is unclear, although the following effects have been proposed. The Fc portion of molecule mediates antibody-dependent cellular cytotoxicity (ADCC) and
complement-dependent cytotoxicity (CDC), which are general regulatory effects on the cell cycle. The rituximab increases MHC II and adhesion molecules lymphocyte function-associated antigens [LFA]-1 and LFA-3, it elicits shedding of CD23, it downregulates the B-cell receptor and it induces apoptosis of CD20+ cells [30]. The combined effect results in the elimination of B cells (including the cancerous ones) from the body, allowing the repopulation with healthy B cells developing from lymphoid stem cells. We could confirm these data on the beneficial effect of added rituximab therapy with our patient who is in complete remission over one year.

We believe that the regular follow-up of patients with SS is of significant importance and the laboratory/radiological and clinical check-ups for malignant transformation are necessary. With the administration of biologicals along with regular cytostatic agents in SS patients with lymphoma, a better outcome can be achieved, and life expectancies become more favourable.

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